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(21) International Application Number: PCT/US97/00128 (22) International Filing Date: 2 January 1997 (02.01.97) (30) Priority Data: 08/582,825 4 January 1996 (04.01.96) US 08/774,414 31 December 1996 (31.12.96) US (60) Parent Application or Grant (63) Related by Continuation US 08/582,825 (CIP) Filed on 4 January 1996 (04.01.96) (71) Applicant (for all designated States except US): AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHANG, Ming-Shi [US/US]; 736 Calle Las Colinas, Newbury Park, CA 91320 (US). WELCHER, Andrew, Avery [US/US]; 786 Capitan Street, Thousand Oaks, CA 91320 (US). FLETCHER, Fred- erick, Addison [US/US]; 5031 Colony Drive, Camarillo, CA 93012 (US).		(74) Agent: PESSIN, Karol, M.; Amgen Inc., Amgen Center, 18- De Havilland Drive, Thousand Oaks, CA 91320-1789 (US) (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, B BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, G HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, L LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, P PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, U UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, S UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, T TM), European patent (AT, BE, CH, DE, DK, ES, FI, F GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (B BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TC  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending a claims and to be republished in the event of the receipt amendments.</i>	
(54) Title: OB PROTEIN RECEPTOR AND RELATED COMPOSITIONS AND METHODS			
(57) Abstract  The present invention relates to a novel class of protein receptors, herein denominated "OB protein receptors" or "OB receptors" which are thought to selectively bind OB protein. As such, the novel OB protein receptor family is provided; as well as novel members of such family. Also provided are nucleic acids, vectors and host cells containing such nucleic acids, related antisense nucleic acid molecules which selectively bind to the OB protein receptor, and related compositions of matter, such as OB receptor protein/OB protein complexes and pharmaceutical compositions. In other aspects, the present invention relates to methods of using the above composition such as therapeutic and/or diagnostic methods, and methods for preparing OB receptor ligands.			
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## OB PROTEIN RECEPTOR AND RELATED COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

5           The present invention relates to OB protein receptors, related compositions and methods of making and using such receptors and related compositions.

BACKGROUND

10           Although the molecular basis for obesity is largely unknown, the identification of the "OB gene" and protein encoded ("OB protein") has shed some light on mechanisms the body uses to regulate body fat deposition. Zhang et al., Nature 372: 425-432 (1994); see  
15 also, the Correction at Nature 374: 479 (1995). The OB protein is active in vivo in both *ob/ob* mutant mice (mice obese due to a defect in the production of the OB gene product) as well as in normal, wild type mice. The biological activity manifests itself in, among other  
20 things, weight loss. See generally, Barinaga, "Obese" Protein Slims Mice, Science 269: 475-476 (1995). See PCT International Publication Number WO 96/05309, "Modulators of Body Weight, Corresponding Nucleic Acids and Proteins, and Diagnostic and Therapeutic Uses  
25 Thereof," herein incorporated by reference.

          The other biological effects of OB protein are not well characterized. It is known, for instance, that in *ob/ob* mutant mice, administration of OB protein results in a decrease in serum insulin levels, and serum  
30 glucose levels. It is also known that administration of OB protein results in a decrease in body fat. This was observed in both *ob/ob* mutant mice, as well as non-obese normal mice. Pelleymounter et al., Science 269: 540-543 (1995); Halaas et al., Science 269: 543-546 (1995). See

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also, Campfield et al., Science 269: 546-549 (1995)  
(Peripheral and central administration of microgram  
doses of OB protein reduced food intake and body weight  
of *ob/ob* and diet-induced obese mice but not in *db/db*  
5 obese mice.) In none of these reports have toxicities  
been observed, even at the highest doses.

Despite the promise of clinical application  
of the OB protein, the mode of action of the OB protein  
in vivo is not clearly elucidated, in part due to the  
10 absence of information on the OB receptor. High affinity  
binding of the OB protein has been detected in the rat  
hypothalamus, reportedly indicating OB receptor loca-  
tion. Stephens et al., Nature 377: 530-532 (1995). The  
*db/db* mouse displays the identical phenotype as the  
15 *ob/ob* mouse, i.e., extreme obesity and Type II diabetes;  
this phenotype is thought to be due to a defective OB  
receptor, particularly since *db/db* mice fail to respond  
to OB protein administration. See Stephens et al.,  
supra.

20 Identification of the OB protein receptor is  
key in determining the pathway of signal transduction.  
Moreover, identification of the OB protein receptor  
would provide powerful application in diagnostic uses,  
for example, to determine if individuals would benefit  
25 from OB protein therapy. Furthermore, the OB receptor  
could be a key component in an assay for determining  
additional molecules which bind to the receptor and  
result in desired biological activity. Further, such  
soluble receptor could enhance or alter the effective-  
30 ness of OB protein (or analog or derivative thereof).

#### SUMMARY OF THE INVENTION

The present invention relates to a novel class  
of protein receptors, herein denominated "OB protein  
35 receptors" or "OB receptors", which are thought to  
selectively bind OB protein. As such, the novel OB

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receptor family is provided, as well as novel members of such family. Also provided are nucleic acids, vectors and host cells containing such nucleic acids, related antisense nucleic acids, molecules which selectively  
5 bind to the OB protein receptor, and related compositions of matter, such as OB receptor protein/OB protein complexes. In other aspects, the present invention relates to methods of using the above compositions, such as therapeutic and/or diagnostic methods, and methods  
10 for preparing OB receptor ligands.

#### DETAILED DESCRIPTION

A novel family of OB receptors is provided. This novel family resulted from identification of a PCR  
15 fragment isolated from a human liver cell cDNA library. The original PCR fragment, from which primers were isolated, contained a "WSXWS" motif, common to cytokine receptors. As illustrated by the working examples below, using this fragment four members of this OB  
20 protein receptor family have been identified. These members, herein designated as "A", "B", and "C", and "D" are identical at amino acid position 1-891 (using the numbering of Seq. ID No. 1), but diverge at position 892 through the C-terminus. They vary in length at the  
25 C-terminus beyond amino acid 891, and the different forms appear to have different tissue distribution.

Using hydrophobicity analysis, the leader sequence is likely to comprise amino acids (Seq. ID. No. 1) 1-21, 1-22, or 1-28. The first amino acid of the  
30 mature protein is likely to be 22 (F), 23 (N) or 29 (T). Most likely, based on analysis of eucaryotic cell expression (CHO cell expression see Example 8, infra), the first amino acid of the mature protein is 22(F). The beginning of the transmembrane domain appears to be  
35 located at position 840 (A) or 842 (L). The end of the transmembrane domain appears to be located at position

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862 (I), 863 (S) or 864 (H). Thus, based on predictions from hydrophobicity analysis, for OB protein binding, at a minimum what is needed is the extracellular domain of the mature protein, amino acids 22, 23 or 29 through amino acids 839 (D) or 841 (G). Therefore, the present class of OB receptor proteins includes those having amino acids (according to Seq. ID No. 1):

- (a) 1-896;
- (b) 22-896;
- 10 (c) 23-896;
- (d) 29-896;
- (e) 1-839;
- (f) 22-839;
- (h) 1-841;
- 15 (i) 22-841;
- (j) 23-841;
- (k) 29-841;
- (l) 1-891;
- (m) 22-891;
- 20 (n) 23-891;
- (o) 29-891;

(p) the amino acids of subparts (l) through (o) having the C-terminal amino acids selected from among:

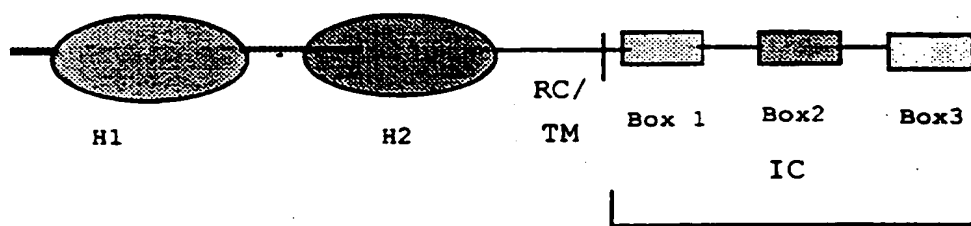
- 25 (i) OB receptor B (Seq. ID No. 3) positions 892-904;
- (ii) OB receptor C (Seq. ID No. 5) positions 892- 958; and,
- (iii) OB receptor D (Seq. ID No. 7) positions 892-1165;
- 30 (q) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, and any of (p) lacking a leader sequence, which have an N-terminal methionyl residue.

35 Also provided herein is what is thought to be a human splice variant of a soluble OB receptor. This

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splice variant includes the extracellular domain at least up to amino acid 798 (of Seq. ID No. 1, for example) and has a unique 6 amino acid C-terminus at positions 799-804: G K F T I L.

5           The functional domains of the OB receptor may be predicted using the information contained in Bazan et al., PNAS-USA 87: 6934-6938 (1990) (incorporated herein by reference). For the present OB receptor, there are two hematopoietin domains, a random coil region, the  
10 transmembrane domain, and the intracellular domain. The overall geography may be illustrated as follows:



Using the information provided by Bazan,  
15 supra, the domains may be predicted, with essentially an error of approximately plus or minus three base pairs (as applied to all amino acid location specified for purposes of identifying the Bazan predicted domains). The precise locations may be determined empirically by  
20 methods known in the art, such as preparing and expressing modified recombinant DNAs. The structural characteristics are thought to be important for maintaining the structural integrity of the molecule, and therefore, to the extent that such structure is  
25 important for function, for functional characteristics as well.

The hematopoietin domains (H1 and H2) are thought to have two fibronectin type 3 repeats each, one set of paired cysteine residues each (thought to form a  
30 disulfide bridge), and one "WSXWS box" (referring to the

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single letter amino acid abbreviation, with "X" being any amino acid). The fibrinectin type 3 domains may be identified by location of a double proline ("PP"), which marks the beginning of the second fibronectin type 3 repeat; the actual beginning of such second fibronectin type 3 repeat is likely to begin about 3 amino acids upstream of that double proline.

The first hematopoietin domain is likely to begin at amino acid 123 (using the numbering according to Seq. ID No. 1, for example), which is an isoleucine residue (I). The last amino acid of the hematopoietin domain is likely to be amino acid 339, which is a lysine (K) residue. The two fibronectin type 3 repeats are likely to be located at (about) amino acids 123 through 235 and 236 through 339. There is a single pair of cysteine residues which likely form a disulfide bridge, located at position 131 and position 142. The "WSXWS box" is located at position 319 through 323.

The second hematopoietin domain is likely to begin at position 428, which is an isoleucine (I) and end at position 642 which is a glycine (G). The paired fibronectin type 3 repeats are located at about position 428 through position 535 and about position 536 through about position 642. One pair of cysteines is located at position 436 and position 447, and the second pair is located at position 473 and 488. The "WSXWS box" is located at position 622-626.

Between the first and the second hematopoietin domain (amino acids 339-428, approximately) is a region of unknown functional significance.

The random coil domain ("RC" between the H2 and the transmembrane domain, "TM") is likely to begin at the amino acid following the end of the second hematopoietin domain, and is likely to end at the beginning of the transmembrane domain. This is likely to be from about amino acid 642 through amino acid 839



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or 841 (with the transmembrane domain beginning at position 840 (A) or 842 (L)). The intracellular domain ("IC") is likely to begin at position 861 (L), 862 (I), 863 (S) or 864 (H).

5           The intracellular domain ("IC") contains three regions, or "boxes," thought to participate in signal transduction (two "JAK" boxes and a single "STAT" box, "Box 1", "Box 2", and "Box 3"). With respect to the numbering of the amino acid positions of the "D" form of  
10 the OB receptor (Seq. ID No.7, below), box 1 is located at amino acid 871 (F) through 878 (P). Box 2 is located at approximately amino acid number 921 (I) through 931 (K). Box 3 on the "D" form is located at approximately position 1141 through 1144 (amino acids YMPQ, as  
15 the "STAT" box is typically a conserved region of "YXXQ" wherein "X" designates any amino acid). The intracellular domain is thought to be responsible for signal transduction. One possible mode of action is via phosphorylation of various residues. See Ihle et al.,  
20 Cell 84: 331-334 (1996) (Review article, herein incorporated by reference.)

One possible mode of action is that upon ligand binding (here, OB protein binding), the OB receptor dimerizes with another receptor. A kinase  
25 ("JAK") binds to box 1, and becomes phosphorylated. (The JAK may already be bound prior to dimerization.) Also, "STATs" bind to box 3 and become phosphorylated on a specific tyrosine. It is thought that this phosphorylation results, probably indirectly, in DNA  
30 binding protein production, which results in altered DNA transcription, and therefore altered expression. As seen below in Example 6, one measurement of the capability of an OB receptor to transduce signal is the degree of phosphorylation of JAK/STAT molecules.

35           The C-terminus region is intracellular (of cell-bound OB receptor). The differences in the C-

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terminus among members of the present OB receptor family may result in differences in signal transduction among the species. Thus, the present OB receptors include at least the extracellular domain which is important for OB protein ligand binding. Nucleic acids encoding the present OB receptors, vectors, and host cells are also provided for herein.

The extracellular domain may be modified and still retain the function of ligand binding, particularly by one or more of the following modifications: (a) the random coil domain (as indicated above, occurring downstream of the second hematopoietic domain through the beginning of the transmembrane domain) may be deleted (this may be approximately positions 642 through 839 or 841); (b) the "WSXWS" box may be modified by (i) substitution of the first serine with another amino acid, particularly conserved in terms of hydrophobicity and/or charge, such as a glycine; (ii) the last serine may be substituted with another amino acid, such as a threonine; (iii) the first tryptophan may be substituted with another amino acid, for example, a tyrosine.

Human genomic DNA encoding OB receptor protein is also provided herein. The genomic DNA has been localized to human chromosome 1P31, which is believed to correspond to mouse chromosome 4, the location of the mouse *db* locus.

Tissue distribution analysis demonstrates the presence of OB receptor nucleic acids is fairly ubiquitous, and particularly noted in the liver. It is also observed in the ovary, and heart; and, to a lesser extent, in small intestine, lung, skeletal muscle, kidney, and, to an even lesser extent, spleen, thymus, prostate, testes, placenta and pancreas (Example 2, below). There may also be one or more forms of the OB receptor present in serum, such as soluble OB receptor,

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which may be complexed to one or more forms of the OB protein.

#### Amino Acid Sequences and Compositions

5           According to the present invention, novel OB protein receptors and DNA sequences coding for all or part of such OB receptors are provided. The present invention provides purified and isolated polypeptide products having part or all of the primary structural  
10           conformation (i.e., continuous sequence of amino acid residues) and one or more of the biological properties (e.g., immunological properties and in vitro biological activity) and physical properties (e.g., molecular weight) of naturally-occurring mammalian OB receptor  
15           including allelic variants thereof. The term "purified and isolated" herein means substantially free of unwanted substances so that the present polypeptides are useful for an intended purpose. For example, one may have a recombinant human OB receptor substantially free  
20           of human proteins or pathological agents. These polypeptides are also characterized by being a product of mammalian cells, or the product of chemical synthetic procedures or of procaryotic or eucaryotic host expression (e.g., by bacterial, yeast, higher plant,  
25           insect and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis. The products of expression in typical yeast (e.g., Saccharomyces cerevisiae), insect, or procaryote (e.g., E. coli) host cells are free of association with  
30           any mammalian proteins. The products of expression in vertebrate (e.g., non-human mammalian (e.g. COS or CHO) and avian) cells are free of association with any human proteins. Depending upon the host employed, and other factors, polypeptides of the invention may be  
35           glycosylated with mammalian or other eucaryotic carbohydrates or may be non-glycosylated. One may modify

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the nucleic acid so that glycosylation sites are included in the resultant polypeptide. One may choose to partially or fully deglycosylate a glycosylated polypeptide. Polypeptides of the invention may also  
5 include an initial methionine amino acid residue (at position -1 with respect to the first amino acid residue of the mature polypeptide).

In addition to naturally-occurring allelic forms of OB receptor, the present invention also  
10 embraces other OB receptor products such as polypeptide analogs of OB receptor and fragments of OB receptor. Following the procedures of the above noted published application by Alton et al. (WO 83/04053), one can readily design and manufacture genes coding for  
15 microbial expression of polypeptides having primary conformations which differ from that herein specified for in terms of the identity or location of one or more residues (e.g., substitutions, terminal and intermediate additions and deletions). Alternately, modifications of  
20 cDNA and genomic genes may be readily accomplished by well-known site-directed mutagenesis techniques and employed to generate analogs and derivatives of OB receptor. Such products would share at least one of the biological properties of mammalian OB receptor but may  
25 differ in others. As examples, projected products of the invention include those which are foreshortened by e.g., deletions; or those which are more stable to hydrolysis (and, therefore, may have more pronounced or longer lasting effects than naturally-occurring); or  
30 which have been altered to delete one or more potential sites for glycosylation (which may result in higher activities for yeast-produced products); or which have one or more cysteine residues deleted or replaced by, e.g., alanine or serine residues and are potentially  
35 more easily isolated in active form from microbial systems; or which have one or more tyrosine residues

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replaced by phenylalanine; or have an altered lysine composition (such as those prepared for purposes of derivatization). Included are those polypeptides with amino acid substitutions which are "conservative" according to acidity, charge, hydrophobicity, polarity, size or any other characteristic known to those skilled in the art. See generally, Creighton, Proteins, W.H. Freeman and Company, N.Y., (1984) 498 pp. plus index, passim. One may make changes in selected amino acids so long as such changes preserve the overall folding or activity of the protein, (see Table 1, below). Small amino terminal extensions, such as an amino-terminal methionine residue, a small linker peptide of up to about 20-25 residues, or a small extension that facilitates purification, such as a poly-histidine tract, an antigenic epitope or a binding domain, may also be present. See, in general Ford et al., Protein Expression and Purification 2: 95-107, 1991, which is herein incorporated by reference.

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Table 1  
Conservative Amino Acid Substitutions

Basic:	arginine lysine histidine
Acidic:	glutamic acid aspartic acid
Polar:	glutamine asparagine
Hydrophobic:	leucine isoleucine valine
Aromatic:	phenylalanine tryptophan tyrosine
Small:	glycine alanine serine threonine methionine

5           Also comprehended are polypeptide fragments duplicating only a part of the continuous amino acid sequence or secondary conformations within OB receptor, which fragments may possess one activity of mammalian (particularly human) OB receptor (e.g., immunological  
10 activity) and not others (e.g., OB protein binding activity).

          Of applicability to OB receptor fragments and polypeptide analogs of the invention are reports of the immunological activity of synthetic peptides which  
15 substantially duplicate the amino acid sequence extant in naturally-occurring proteins, glycoproteins and nucleoproteins. More specifically, relatively low

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molecular weight polypeptides have been shown to participate in immune reactions which are similar in duration and extent to the immune reactions of physiologically significant proteins such as viral antigens, polypeptide hormones, and the like. Included among the immune reactions of such polypeptides is the provocation of the formation of specific antibodies in immunologically active animals. See, e.g., Lerner et al., Cell 23: 309-310 (1891); Ross et al., Nature 294: 654-656 (1891); Walter et al., PNAS-USA 77: 5197-5200 (1980); Lerner et al., PNAS-USA, 78: 3403-3407 (1891); Walter et al., PNAS-USA 78: 4882-4886 (1891); Wong et al., PNAS-USA 79: 5322-5326 (1982); Baron et al., Cell 28: 395-404 (1982); Dressman et al., Nature 295: 185-160 (1982); and Lerner, Scientific American 248: 66-74 (1983). See, also, Kaiser et al. Science 223: 249-255 (1984) relating to biological and immunological activities of synthetic peptides which approximately share secondary structures of peptide hormones but may not share their primary structural conformation. The present invention also includes that class of polypeptides coded for by portions of the DNA complementary to the protein-coding strand of the human cDNA or genomic DNA sequences of OB receptor i.e., "complementary inverted proteins" as described by Tramontano et al. Nucleic Acid Res. 12: 5049-5059 (1984). Polypeptides or analogs thereof may also contain one or more amino acid analogs, such as peptidomimetics.

Thus, the present class of OB receptor proteins includes those having amino acids (according to Seq. ID No. 1):

- (a) 1-896;
- (b) 22-896;
- (c) 23-896;
- (d) 29-896
- (e) 1-839;

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- 5 (f) 22-839;  
(g) 29-839;  
(h) 1-841;  
(i) 22-841;  
(j) 23-841;  
(k) 29-841;  
(l) 1-891;  
(m) 22-891;  
(n) 23-891;  
10 (o) 29-891;

(p) the amino acids of subparts (l) through (o) having the C-terminal amino acid sequence beginning at position 892 of OB receptor B (Seq. ID No. 3) or C (Seq. ID. No. 5);

- 15 (q) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, and any of (p) lacking a leader sequence, which have an N-terminal methionyl residue.

Also provided is a longer form of an OB receptor protein, herein denominated the "D" form, which  
20 has an amino acid sequence selected from among (according to Seq. ID No. 7):

- (a) amino acids 1-1165;  
(b) amino acids 22-1165;  
(c) amino acids 23-1165;  
25 (d) amino acids 29-1165;  
(e) amino acids of subparts (b), (c) or (d) having an N-terminal methionyl residue.

As set forth above, one may prepare soluble receptor by elimination of the transmembrane and intra-  
30 cellular regions. Examples of soluble receptors include those set forth in Seq. ID Nos. 10 and 13. What is thought to be a native, secreted form of a soluble human OB receptor is also provided herein. This form of OB receptor protein has an amino acid sequence selected  
35 from among (according to Seq. ID No. 13):

- (a) amino acids 1-804;



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- (b) amino acids 22-804;
  - (c) amino acids 23-804;
  - (d) amino acids 29-804; and,
  - (e) amino acids of subparts (b), (c) or
- 5 (d) having an N-terminal methionyl residue.

In addition, since the C-terminus region of the above polypeptides diverges at position 892 (with respect to Seq. ID Nos. 1, 3, 5, 7 and 13) one may desire to prepare only the polypeptides which are

10 divergent:

- (a) those having only amino acids 892-896 of Seq. ID No. 1;
  - (b) those having only amino acids 892-904 of Seq. ID No. 3;
  - 15 (c) those having only amino acids 892-958 of Seq. ID No. 5;
  - (d) those having only amino acids 892-1165 of Seq. ID No. 7; and,
  - (e) those having only amino acids 799-804
- 20 of Seq. ID No. 13.

The above polypeptides which have an extracellular domain may be modified, as indicated above, and still retain the function of ligand binding. Such modification may include one or more of the

25 following:

- (a) the random coil domain (as indicated above, occurring downstream of the second hematopoietic domain through the beginning of the transmembrane domain) may be deleted (this may be approximately
- 30 positions 642 through 839 or 841);
- (b) the "WSXWS" box may be modified by
    - (i) substitution of the first serine with another amino acid, particularly conserved in terms of hydrophobicity and/or charge, such as a glycine; (ii) the last serine
- 35 may be substituted with another amino acid, such as a threonine; (iii) the first tryptophan may be

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substituted with another amino acid, for example, a tyrosine.

Thus, the present polypeptides include (according to the numbering of Seq. ID No. 7):

- 5 (a) 1-896;  
(b) 22-896;  
(c) 23-896;  
(d) 29-896  
(e) 1-839;  
10 (f) 22-839;  
(g) 29-839;  
(h) 1-841;  
(i) 22-841;  
(j) 23-841;  
15 (k) 29-841;  
(l) 1-891;  
(m) 22-891;  
(n) 23-891;  
(o) 29-891;  
20 (p) the amino acids of subparts (l) through (o) having the C-terminal amino acids selected from the C-terminal amino acids of OB receptor B (Seq. ID No. 3), C (Seq. ID. No. 5) and D (Seq ID No. 7);  
(q) the amino acids (according to Seq. ID  
25 No. 13) selected from the group consisting of 22-804; 23-804 and 29-804;  
(r) amino acids of subparts b, c, d, f, g, i, j, k, m, n, o, any of (p) lacking a leader sequence, and (q) which have an N-terminal methionyl  
30 residue; and  
(s) amino acids of subparts (a) through (r) which above having at least one of the following modifications:  
(i) for amino acids of subparts (a)  
35 through (p) and those of subpart (r) which are not amino acids according to subpart (q), deletion of (or

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substitution of amino acid(s) or other modifications of)  
a random coil domain sequence selected from

(a) 640 through 839 (using  
the numbering according to Seq. ID No. 1);

5

(b) 641 through 839;

(c) 642 through 839;

(d) 640 through 841;

(e) 641 through 841; and

(f) 642 through 841;

10

(ii) for amino acids of subpart (q)  
and those of subpart (r) which contain the sequence of  
subpart (q), deletion of of (or substitution of amino  
acid(s) or other modifications of) a random coil domain  
sequence selected from among:

15

(a) 640 through 804;

(b) 641 through 804; and,

(c) 642 through 804;

and,

(iii) modification of a "WSXWS"

20

sequence which is

(a) substitution of the first  
serine with another amino acid, particularly conserved  
in terms of hydrophobicity and/or charge, such as a  
glycine;

25

(b) substitution of the last  
serine with another amino acid, such as a threonine;  
and

(c) substitution of the first  
tryptophan with another amino acid, for example, a  
tyrosine.

30

One may modify the OB receptor to create a  
fusion molecule with other peptide sequence. For  
example, if one desired to "tag" the OB receptor with an  
immunogenic peptide, one could construct a DNA which  
would result in such fusion protein. The tag may be at  
the N-terminus. Also, since it is apparent that the

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C-terminus is not necessary for ligand binding activity, one may chemically modify the C-terminus of, for example, a soluble OB receptor. One may desire, for example, a preparation whereby one or more polymer  
5 molecules such as polyethylene glycol molecules are attached. Thus, another aspect of the present invention is chemically modified OB receptor protein (also further described infra).

An example of such "tag" is provided herein  
10 using the C-terminus of a recombinant soluble OB receptor. Seq. ID No. 12 provides a "FLAG-tag" version of such soluble OB receptor (the nucleic acid sequence is provided, which may be transcribed to prepare the polypeptide). Such "FLAG-tag" may also be attached to  
15 the N-terminus or other region of an OB receptor protein. This type of "tagging" is useful to bind the protein using reagents, such as antibodies, which are selective for such tag. Such binding may be for detection of the location or amount of protein, or for  
20 protein capturing processes where, for example, an affinity column is used to bind the tag, and thus the desired protein. Other types of detectable labels, such as radioisotopes, light-emitting (e.g., fluorescent or phosphorescent compounds), enzymatically cleavable,  
25 detectable antibody (or modification thereof), or other substances may be used for such labelling of the present proteins. Detecting protein via use of the labels may be useful for identifying the presence or amount of OB receptor protein or a compound containing such protein  
30 (e.g., OB protein complexed to OB receptor). Moreover, such labelled protein may be useful for distinguishing exogenous OB receptor protein from the endogenous form.

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Nucleic Acids

Novel nucleic acid sequences of the invention include sequences useful in securing expression in procaryotic or eucaryotic host cells of polypeptide products having at least a part of the primary structural conformation and one or more of the biological properties of recombinant human OB receptor. The nucleic acids may be purified and isolated, so that the desired coding region is useful to produce the present polypeptides, for example, or for diagnostic purposes, as described more fully below. DNA sequences of the invention specifically comprise: (a) any of the DNA sequences set forth in Seq. ID No. 2, 4, 6, 8, 9, 11, 12, and 14 (and complementary strands); (b) a DNA sequence which hybridizes (under hybridization conditions disclosed in the cDNA library screening section below, using the 300 bp PCR fragment as described to selectively hybridize to a cDNA encoding an OB receptor protein in a human liver cDNA library, or equivalent conditions or more stringent conditions) to the DNA sequence in subpart (a) or to fragments thereof; and (c) a DNA sequence which, but for the degeneracy of the genetic code, would hybridize to the DNA sequence in subpart (a). Specifically comprehended in parts (b) and (c) are genomic DNA sequences encoding allelic variant forms of human OB receptor and/or encoding OB receptor from other mammalian species, and manufactured DNA sequences encoding OB receptor, fragments of OB receptor, and analogs of OB receptor which DNA sequences may incorporate codons facilitating transcription and translation of messenger RNA in microbial hosts. Such manufactured sequences may readily be constructed according to the methods of Alton et al., PCT published application WO 83/04053.

- 20 -

Genomic DNA, such as that of Seq. ID No. 9, encoding the present OB receptors may contain additional non-coding bases, or introns, and such genomic DNAs are obtainable by hybridizing all or part of the cDNA, 5 illustrated in Seq. ID Nos. 2, 4, 6, 8, 11, and 14 to a genomic DNA source, such as a human genomic DNA library. Such genomic DNA will encode functional OB receptor polypeptide; however, use of the cDNAs may be more practicable in that, since only the coding region is 10 involved, recombinant manipulation is facilitated. The intron/exon location of genomic DNA is set forth in Seq. ID No. 9, infra.

Nucleic acid sequences include the incorporation of codons which enhance expression by 15 selected nonmammalian hosts; the provision of sites for cleavage by restriction endonuclease enzymes; and the provision of additional initial, terminal or intermediate DNA sequences which facilitate construction of cloning and/or expression vectors.

20 The present invention also provides DNA sequences coding for polypeptide analogs or derivatives of OB receptor which differ from naturally-occurring forms in terms as described above. The leader sequence DNA may be substituted with another leader sequence for 25 ease in expression or for other purposes.

Also, one may prepare antisense nucleic acids against the present DNAs. Such antisense nucleic acids may be useful in modulating the effects of OB receptor protein in vivo. For example, one may prepare an 30 antisense nucleic acid which effectively disables the ability of a cell to produce OB receptor by binding to the nucleic acid which encodes such OB receptor.

DNA sequences of the invention are also suitable materials for use as labeled probes in 35 isolating human genomic DNA encoding OB receptor, as mentioned above, and related proteins as well as cDNA

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and genomic DNA sequences of other mammalian species. DNA sequences may also be useful in various alternative methods of protein synthesis (e.g., in insect cells) or, as described infra, in genetic therapy in humans and  
5 other mammals. DNA sequences of the invention are expected to be useful in developing transgenic mammalian species which may serve as eucaryotic "hosts" for production of OB receptor and OB receptor products in quantity. See, generally, Palmiter et al., Science 222:  
10 809-814 (1983).

#### Vectors and Host Cells

According to another aspect of the present invention, the DNA sequences described herein which  
15 encode OB receptor polypeptides are valuable for the information which they provide concerning the amino acid sequence of the mammalian protein which have heretofore been unavailable. Put another way, DNA sequences provided by the invention are useful in generating new  
20 and useful viral and circular plasmid DNA vectors, new and useful transformed and transfected procaryotic and eucaryotic host cells (including bacterial cells, yeast cells, insect cells, and mammalian cells grown in culture), and new and useful methods for cultured growth  
25 of such host cells capable of expression of OB receptor and its related products.

The DNA provided herein (or corresponding RNAs) may also be used for gene therapy for, example, treatment of conditions characterized by the  
30 overexpression of OB protein, such as anorexia or cachexia. Alternatively, gene therapy may be used in cases where increased sensitivity to OB protein is desired, such as in cases where an individual has a condition characterized by OB protein receptors  
35 defective in ability to bind or retain the binding of OB protein. Currently, vectors suitable for gene therapy

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(such as retroviral or adenoviral vectors modified for gene therapy purposes and of purity and pharmaceutical acceptability) may be administered for delivery into the lung, for example. Such vectors may incorporate nucleic acid encoding the present polypeptides for expression in  
5 a desired location. Gene therapy may involve more than one gene for a desired protein or different desired proteins.

Alternatively, one may use no vector so as to  
10 facilitate relatively stable presence in the host. For example, homologous recombination of a DNA as provided herein or of a suitable transcription or translation control region may facilitate integration into or expression from a host genome. (This may be performed  
15 for production purposes as well, e.g., U.S. Patent No. 5,272,071 and WO 91/09955.) The nucleic acid may be placed within a pharmaceutically acceptable carrier to facilitate cellular uptake, such as a lipid solution carrier (e.g., a charged lipid), a liposome, or  
20 polypeptide carrier (e.g., polylysine). A review article on gene therapy is Verma, Scientific American, November 1990, pages 68-84 which is herein incorporated by reference.

Thus, the present invention provides for a  
25 population of cells expressing an OB receptor of the present OB receptor family. Such cells are suitable for transplantation or implantation into an individual for therapeutic purposes. For example, one may prepare a population of cells to overexpress OB receptor (such as  
30 one identified in the Sequence ID's or otherwise denoted herein), or to express a desired form of OB receptor, such as one which is particularly sensitive to OB protein (i.e., a form which has a desired capacity for signal transduction). One may then implant such cells  
35 into an individual to increase that individual's sensitivity to OB protein. Such cells may, for example,



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be liver cells, bone marrow cells, or cells derived from umbilical cord. Alternatively, one may wish to use overexpressing circulating cells such as blood progenitor cells, T cells or other blood cells. For humans, human cells may be used. Cells may be in the form of tissue. Such cells may be cultured prior to transplantation or implantation. Such OB receptor overexpression, or expression of particularly sensitive forms of OB receptor may be accomplished by, for example, altering the regulatory mechanism for expression of OB receptor, such as using homologous recombination techniques as described supra. Thus, provided is a population of host cells modified so that expression of endogenous OB receptor DNA is enhanced.

The cells to be transferred to the recipient may be cultured using one or more factors affecting the growth or proliferation of such cells if appropriate. Hematopoietic factors may be used in culturing hematopoietic cells. Such factors include G-CSF, EPO, MGDF, SCF, Flt-3 ligand, interleukins (e.g., IL1-IL13), GM-CSF, LIF, and analogs and derivatives thereof as available to one skilled in the art.

Nerve cells, such as neurons or glia, may also be used, and these may be cultured with neurotrophic factors such as BDNF, CNTF, GDNF, NT3, or others.

There may be a co-gene therapy involving the transplantation of cells expressing more than one desired protein. For example, cells expressing OB receptor protein may be used in conjunction, simultaneously or in serriatim with cells expressing OB protein.

For gene therapy dosages, one will generally use between one copy and several thousand copies of the present nucleic acid per cell, depending on the vector, the expression system, the age, weight and condition of the recipient and other factors which will be apparent

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to those skilled in the art. The cellular delivery of such protein may be designed to last for a selected period of time, such as a period of days, weeks, months or years. At the end of the effective time period, the recipient of such transformed cells may receive another "dose" (e.g., transplantation of cells). Cells may be selected for their lifespan, their time period of expression of the desired protein, or their ability to be reisolated from an individual (i.e., for blood cells, leukaphoresis may be used to retrieve transformed cells using markers present on the cell surface). Vectors may be similiarly designed using, for example, viruses which have a known period of expression of DNAs contained therein.

The desired cells or vectors may be stored using techniques, such as freezing, available to those in the art.

Thus, the present invention also contemplates a method for administering OB receptor protein to an individual, wherein the source of said OB receptor protein is selected from (i) a population of cells expressing OB receptor protein and (ii) a population of vectors expressing OB receptor protein. Said OB receptor protein may be selected from among those described herein. Said vectors may be virus vectors capable of infecting human cells. Said cells may be selected from among tissue or individual cells. Said individual cells may be selected from among adipocytes, fibroblasts, bone marrow cells, peripheral blood progenitor cells, red blood cells, and white blood cells, including T cells and nerve cells. Said population of cells or vectors may be co-administered with a population of cells or vectors which express OB protein or another desired protein. Said cells or vectors may be stored for use in an individual. Storage may be by freezing

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Complexes

In addition to the OB receptor protein as described herein, one may prepare complexes of OB  
5 receptor protein and OB protein, analog or derivative.

The OB protein may be selected from those described in PCT publication WO 96/05309, above and hereby incorporated by reference in its entirety. Figure 3 of that publication (Seq. ID No. 4, as cited  
10 therein) depicts the full deduced amino acid sequence derived for the human OB gene. The amino acids are numbered from 1 to 167. A signal sequence cleavage site is located after amino acid 21 (Ala) so that the mature protein extends from amino acid 22 (Val) to amino acid  
15 167 (Cys). For the present disclosure, a different numbering is used herein, where the amino acid position 1 is the Valine residue which is at the beginning of the mature protein.

Generally, the OB protein for use will be  
20 capable of complexing to the OB protein receptor selected. Thus, one may empirically test the binding capability (to all or part of the extracellular domain of the OB receptor as indicated above) to determine which OB protein forms may be used. Generally,  
25 modifications generally applicable as indicated above for OB receptor protein may also be applied here, and that disclosure is incorporated by reference here. As set forth in WO 96 05309, OB protein in its native form, or fragments (such as enzyme cleavage products) or other  
30 truncated forms, analogs, and derivatives all retain biological activity. Such forms may be used so long as the form binds to at least a portion of the extracellular domain of the present OB receptor proteins.

35 An effective amount of an OB protein, analog or derivative thereof may be selected from among

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according to the amino acid sequence as presented in PCT WO 96/05309, Figure 3 numbered so that the first amino acid of the mature protein is number 1:

(a) the amino acid sequence 1-146,  
5 optionally lacking a glutaminy residue at position 28,  
and further optionally having a methionyl residue at the N-terminus;

(b) an amino acid sequence of subpart  
(a) having a different amino acid substituted in one or  
10 more of the following positions: 4, 8, 32, 33, 35, 48,  
50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97,  
100, 102, 105, 106, 107, 108, 111, 112, 118, 136, 138,  
142, and 145;

(c) a truncated OB protein analog  
15 selected from among: (using the numbering of subpart (a)  
above):

- (i) amino acids 98-146
- (ii) amino acids 1-32
- (iii) amino acids 1-35
- 20 (iv) amino acids 40-116
- (v) amino acids 1-99 and 112-146
- (vi) amino acids 1-99 and 112-146.

having one or more of amino acids 100-111  
sequentially placed between amino acids 99 and 112;  
25 and,

- (vii) the truncated OB analog of  
subpart (i) having one or more of amino acids 100,  
102, 105, 106, 107, 108, 111, 112, 118, 136, 138,  
142, and 145 substituted with another amino acid;
- 30 (viii) the truncated analog of subpart  
(ii) having one or more of amino acids 4, 8 and 32  
substituted with another amino acid;
- (ix) the truncated analog of subpart  
(iv) having one or more of amino acids 50, 53, 60,  
35 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 100, 102,

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105, 106, 107, 108, 111 and 112 replaced with another amino acid;

5 (x) the truncated analog of subpart (v) having one or more of amino acids 4, 8, 32, 33, 35, 48, 50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 112, 118, 136, 138, 142, and 145 replaced with another amino acid;

10 (xi) the truncated analog of subpart (vi) having one or more of amino acids 4, 8, 32, 33, 35, 48, 50, 53, 60, 64, 66, 67, 68, 71, 74, 77, 78, 89, 97, 100, 102, 105, 106, 107, 108, 111, 112, 118, 136, 138, 142, and 145 replaced with another amino acid;

15 (xii) the truncated analog of any of subparts (i)-(xi) having an N-terminal methionyl residue; and

(d) the OB protein or analog derivative of any of subparts (a) through (c) comprised of a chemical moiety connected to the protein moiety;

20 (e) a derivative of subpart (d) wherein said chemical moiety is a water soluble polymer moiety;

(f) a derivative of subpart (e) wherein said water soluble polymer moiety is polyethylene glycol;

25 (g) A derivative of subpart (f) wherein said water soluble polymer moiety is a polyamino acid moiety;

30 (h) a derivative of subpart (g) wherein said water soluble polymer moiety is attached at solely the N-terminus of said protein moiety;

(i) an OB protein, analog or derivative of any of subparts (a) through (h) in a pharmaceutically acceptable carrier.

35 OB proteins, analogs and related molecules are also reported in the following publications; however, no

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representation is made with regard to the activity of any composition reported:

5 U.S. Patent Nos. 5,521,283; 5,532,336;  
5,552,522; 5,552,523; 5,552,524; 5,554,727;  
5,559,208; 5,563,243; 5,563,244; 5,563,245;  
5,567,678; 5,567,803; 5,569,744; 5,569,743  
(all assigned to Eli Lilly and Company);  
PCT WO96/23517; WO96/23515; WO96/23514;  
WO96/24670; WO96/23513; WO96/23516;  
10 WO96/23518; WO96/23519; WO96/23520;  
WO96/23815; WO96/24670; WO96/27385 (all  
assigned to Eli Lilly and Company);  
PCT WO96/22308 (assigned to Zymogenetics);  
PCT WO96/29405 (assigned to Ligand  
15 Pharmaceuticals, Inc.);  
PCT WO96/31526 (assigned to Amylin  
Pharmaceuticals, Inc.);  
PCT WO96/34885 (assigned to Smithkline Beecham  
PLC);  
20 PCT WO96/35787 (assigned to Chiron);  
EP 0 725 079 (assigned to Eli Lilly and  
Company);  
EP 0 725 078 (assigned to Eli Lilly and  
Company);  
25 EP 0 736 599 (assigned to Takeda);  
EP 0 741 187 (assigned to F. Hoffman LaRoche).

To the extent these references provide for  
useful OB proteins or analogs or derivatives thereof, or  
30 associated compositions or methods, such compositions  
and/or methods may be used in conjunction with the  
present OB receptor proteins, such as for co-  
administration (together or separately, in a selected  
dosage schedule) or by complexing compositions to the  
35 present OB protein receptors. With the above provisos,  
these publications are herein incorporated by reference.

### Derivatives and Formulations

The present OB protein receptor and/or OB protein (herein the term "protein" is used to include "peptide" and OB protein or receptor analogs, such as those recited infra, unless otherwise indicated) may also be derivatized by the attachment of one or more chemical moieties to the protein moiety. If the present pharmaceutical compositions contain as the active ingredient a complex of OB protein receptor and OB protein, one or both of such proteins may be derivatized. The chemically modified derivatives may be further formulated for intraarterial, intraperitoneal, intramuscular, subcutaneous, intravenous, oral, nasal, pulmonary, topical or other routes of administration. Chemical modification of biologically active proteins has been found to provide additional advantages under certain circumstances, such as increasing the stability and circulation time of the therapeutic protein and decreasing immunogenicity. See U.S. Patent No. 4,179,337, Davis et al., issued December 18, 1979. For a review, see Abuchowski et al., in Enzymes as Drugs. (J.S. Holcerberg and J. Roberts, eds. pp. 367-383 (1891)). A review article describing protein modification and fusion proteins is Francis, Focus on Growth Factors 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20, OLD, UK).

Preferably, for therapeutic use of the end-product preparation, the chemical moiety for derivatization will be pharmaceutically acceptable. A polymer may be used. One skilled in the art will be able to select the desired polymer based on such considerations as whether the polymer/protein conjugate will be used therapeutically, and if so, the desired dosage, circulation time, resistance to proteolysis, and

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other considerations. For the present proteins and peptides, the effectiveness of the derivatization may be ascertained by administering the derivative, in the desired form (i.e., by osmotic pump, or by injection or  
5 infusion, or, further formulated for oral, pulmonary or nasal delivery, for example), and observing biological effects as described herein.

The chemical moieties suitable for derivatization may be selected from among various water  
10 soluble polymers. The polymer selected should be water soluble so that the protein to which it is attached so that it is miscible in an aqueous environment, such as a physiological environment. The water soluble polymer may be selected from the group consisting of, for  
15 example, polyethylene glycol, copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids  
20 (either homopolymers or random or non-random copolymers (see supra regarding fusion molecules), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols,  
25 polystyrenemaleate and polyvinyl alcohol. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water.

Fusion proteins may be prepared by attaching polyaminoacids to the OB protein receptor or OB protein  
30 (or analog or complex) moiety. For example, the polyamino acid may be a carrier protein which serves to increase the circulation half life of the protein. For the present therapeutic or cosmetic purposes, such polyamino acid should be those which do not create  
35 neutralizing antigenic response, or other adverse response. Such polyamino acid may be selected from the



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group consisting of serum album (such as human serum albumin), an antibody or portion thereof (such as an antibody constant region, sometimes called "Fc") or other polyamino acids. As indicated below, the location of attachment of the polyamino acid may be at the N-terminus of the OB protein moiety, or other place, and also may be connected by a chemical "linker" moiety to the OB protein.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 2 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

The number of polymer molecules so attached may vary, and one skilled in the art will be able to ascertain the effect on function. One may mono-derivatize, or may provide for a di-, tri-, tetra- or some combination of derivatization, with the same or different chemical moieties (e.g., polymers, such as different weights of polyethylene glycols). The proportion of polymer molecules to protein (or peptide) molecules will vary, as will their concentrations in the reaction mixture. In general, the optimum ratio (in terms of efficiency of reaction in that there is no excess unreacted protein or polymer) will be determined by factors such as the desired degree of derivatization (e.g., mono, di-, tri-, etc.), the molecular weight of

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the polymer selected, whether the polymer is branched or unbranched, and the reaction conditions.

The chemical moieties should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art. E.g., EP 0 401 384 herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20: 1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule (or other chemical moiety) may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residue. Those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecule(s) (or other chemical moiety). Preferred for therapeutic manufacturing purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group. Attachment at residues important for receptor binding should be avoided if receptor binding is desired.

One may specifically desire N-terminally chemically modified protein. Using polyethylene glycol as an illustration of the present compositions, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining

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the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective N-terminal chemical modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. See PCT WO 96/11953, herein incorporated by reference. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved. For example, one may selectively N-terminally pegylate the protein by performing the reaction at a pH which allows one to take advantage of the  $pK_a$  differences between the  $\epsilon$ -amino group of the lysine residues and that of the  $\alpha$ -amino group of the N-terminal residue of the protein. By such selective derivatization, attachment of a polymer to a protein is controlled: the conjugation with the polymer takes place predominantly at the N-terminus of the protein and no significant modification of other reactive groups, such as the lysine side chain amino groups, occurs. Using reductive alkylation, the polymer may be of the type described above, and should have a single reactive aldehyde for coupling to the protein. Polyethylene glycol propionaldehyde, containing a single reactive aldehyde, may be used.

An N-terminally chemically modified derivative is preferred (over other forms of chemical modification) for ease in production of a therapeutic. N-terminal chemical modification ensures a homogenous product as characterization of the product is simplified relative to di-, tri- or other multi-derivatized products. The use of the above reductive alkylation process for

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preparation of an N-terminally chemically modified product is preferred for ease in commercial manufacturing.

In yet another aspect of the present invention, provided are methods of using pharmaceutical compositions of the proteins, and derivatives. Such pharmaceutical compositions may be for administration by injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, comprehended by the invention are pharmaceutical compositions comprising effective amounts of protein or derivative products of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. See, e.g., PCT W096/29989, Collins et al., "Stable protein: phospholipid compositions and methods," published October 3, 1996, herein incorporated by reference. Hylauronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in

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liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

5                   Specifically contemplated are oral dosage forms of the above derivatized proteins. Protein may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least  
10 one moiety to the protein (or peptide) molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the protein and increase in circulation  
15 time in the body. See PCT WO95/21629, Habberfield, "Oral Delivery of Chemically Modified Proteins" (published August 17, 1995) herein incorporated by reference, and U.S. Patent No. 5,574,018, Habberfield et al., "Conjugates of Vitamin B12 and Proteins," issued  
20 November 12, 1996, herein incorporated by reference.

Also contemplated herein is pulmonary delivery of the present protein, or derivative thereof. The protein (derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung  
25 epithelial lining to the blood stream. See, PCT WO94/20069, Niven et al., "Pulmonary administration of granulocyte colony stimulating factor," published September 15, 1994, herein incorporated by reference.

Nasal delivery of the protein (or analog or  
30 derivative) is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those  
35 with absorption enhancing agents, such as dextran or

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cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

#### Dosages

- 5                   One skilled in the art will be able to ascertain effective dosages by administration and observing the desired therapeutic effect. Preferably, the formulation of the molecule or complex in a pharmaceutical composition will be such that between  
10   about .10 µg/kg/day and 10 mg/kg/day will yield the desired therapeutic effect. The effective dosages may be determined using diagnostic tools over time. For example, a diagnostic for measuring the amount of OB protein or OB receptor protein in the blood (or plasma  
15   or serum) may first be used to determine endogenous levels of OB protein (or receptor). Such diagnostic tool may be in the form of an antibody assay, such as an antibody sandwich assay. The amount of endogenous OB receptor protein (such as soluble receptor) is  
20   quantified initially, and a baseline is determined. The therapeutic dosages are determined as the quantification of endogenous and exogenous OB receptor protein (that is, protein, analog or derivative found within the body, either self-produced or administered) is continued over  
25   the course of therapy. The dosages may therefore vary over the course of therapy, with a relatively high dosage being used initially, until therapeutic benefit is seen, and lower dosages used to maintain the therapeutic benefits.
- 30                   During an initial course of therapy of an obese person, dosages may be administered whereby weight loss and concomitant fat tissue decrease increase is achieved. Once sufficient weight loss is achieved, a dosage sufficient to prevent re-gaining weight, yet  
35   sufficient to maintain desired weight or fat mass may be administered. These dosages can be determined

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empirically, as the effects of OB protein are reversible. E.g., Campfield et al., Science 269: 546-549 (1995) at 547. Thus, if a dosage resulting in weight loss is observed when weight loss is not desired, one  
5 would administer a lower dose, yet maintain the desired weight.

#### Therapeutic Compositions and Methods

The present OB receptor proteins, alone, or in  
10 combination with an OB protein, and nucleic acids may be used for methods of treatment, or for methods of manufacturing medicaments for treatment. Such treatment includes conditions characterized by excessive  
production of OB protein, wherein the present OB  
15 receptors, particularly in soluble form, may be used to complex to and therefore inactivate such excessive OB protein. Or, such OB receptor protein, particularly in soluble form, may act to protect the activity of OB protein. While not wishing to be bound by theory, one  
20 may postulate that OB protein receptor agonist activity may be accomplished by a protective effect achieved when OB protein receptor (particularly soluble receptor) is complexed to OB protein. Such effect may prolong the serum half life of OB protein in vivo. Such treatments  
25 may be accomplished by preparing soluble receptor (e.g., use of an extracellular domain as described supra) and administering such composition to an individual in need thereof or by preparation of a population of cells containing or expressing such OB receptor, and  
30 transplanting such cells into the individual in need thereof.

The present OB receptors may also be used for treatment of those having defective OB receptors. For example, one may treat an individual having defective OB  
35 receptors by preparation of a population of cells containing such non-defective OB receptor, and

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transplanting such cells into an individual. Or, an individual may have an inadequate number of OB receptors, and cells containing such receptors may be transplanted in order to increase the number of OB  
5 receptors available to an individual.

The present OB receptor proteins and related compositions such as OB receptor protein/OB protein complex, provide for weight loss, fat loss, increase in lean mass, increase in insulin sensitivity, increase in  
10 overall strength, increase in red blood cells (and oxygenation in the blood), decrease in bone resorption or osteoporosis, decreased or maintained serum cholesterol level, decreased or maintained triglyceride (LDL or VLDL) levels, prevention or reduction in  
15 arterial plaque formation, treatment of hypertension, and prevention or reduction of gall stone formation. As body fat composition may be correlated with certain types of cancers, the present compositions may be useful for the prevention or amelioration of certain types of  
20 cancers. The present invention also includes methods for manufacture of a medicament for use in conjunction with the cosmetic/therapeutic conditions described herein, containing at least one of the present compositions.

25 The present compositions and methods may be used in conjunction with other medicaments, such as those useful for the treatment of diabetes (e.g., insulin or analogs thereof, thiazolidinediones or other antihyperglycemic agents, and possibly amylin or  
30 antagonists thereof), cholesterol and blood pressure lowering medicaments (such as those which reduce blood lipid levels or other cardiovascular medicaments), and activity increasing medicaments (e.g., amphetamines). Appetite suppressants may also be used (such as  
35 serotonin modulators and neuropeptide Y antagonists).



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Such administration may be simultaneous or may be in  
seriatim.

In addition, the present methods may be used  
in conjunction with surgical procedures, such as  
5 cosmetic surgeries designed to alter the overall  
appearance of a body (e.g., liposuction or laser  
surgeries designed to reduce body mass, or implant  
surgeries designed to increase the appearance of body  
mass). The health benefits of cardiac surgeries, such  
10 as bypass surgeries or other surgeries designed to  
relieve a deleterious condition caused by blockage of  
blood vessels by fatty deposits, such as arterial  
plaque, may be increased with concomitant use of the  
present compositions and methods. Methods to eliminate  
15 gall stones, such as ultrasonic or laser methods, may  
also be used either prior to, during or after a course  
of the present therapeutic methods. Furthermore, the  
present methods may be used as an adjunct to surgeries  
or therapies for broken bones, damaged muscle, or other  
20 therapies which would be improved by an increase in lean  
tissue mass.

In yet another aspect, the present invention  
provides for methods of manufacture of a medicament for  
the treatment of obesity, type II diabetes, excess blood  
25 lipid, or cholesterol levels, increasing sensitivity to  
insulin, increasing lean mass, and other conditions as  
set forth above. Also provided are solely cosmetic  
treatments for individuals wishing to improve appearance  
by weight loss, and more specifically, loss of fat  
30 deposits, even in the absence of any therapeutic  
benefit.

#### Diagnostic Compositions and Methods

As indicated supra, polypeptide products of  
35 the invention may be "labeled" by association with a  
detectable marker substance (e.g., radiolabeled with

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125I, fluorescent, chemiluminescent, enzyme) to provide reagents useful in detection and quantification of OB receptor (or complexes) in solid tissue and fluid samples such as blood or urine. Nucleic acid products of the invention may also be labeled with detectable markers (such as radiolabels and non-isotopic labels such as biotin) and employed in hybridization processes to locate the human OB receptor gene position and/or the position of any related gene family in a chromosomal map. Nucleic acid sequences which selectively bind the human OB receptor gene are useful for this purpose. They may also be used for identifying human OB receptor gene disorders at the DNA level and used as gene markers for identifying neighboring genes and their disorders. Such nucleic acid sequences may be used for detection or measurement of OB receptor mRNA level from a biological sample. Contemplated herein are kits containing such labelled materials.

The protein and/or nucleic acids provided herein may also be embodied as part of a kit or article of manufacture. Contemplated is an article of manufacture comprising a packaging material and one or more preparations of the presently provided compositions. Such packaging material will comprise a label indicating that the protein or nucleic acid preparation is useful for detecting and/or quantifying the amount of OB receptor in a biological sample, or OB receptor defects in a biological sample. As such, the kit may optionally include materials to carry out such testing, such as reagents useful for performing DNA or RNA hybridization analysis, or PCR analysis on blood, urine, or tissue samples.

A further embodiment of the invention is selective binding molecules, such as monoclonal antibodies selectively binding OB receptor. The

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hybridoma technique described originally by Kohler and Milstein Eur. J. Immunol. 6, 511-519 (1976) has been widely applied to produce hybrid cell lines that secrete high levels of monoclonal antibodies against many specific antigens. Recombinant antibodies, (see Huse et al., Science 246: 1275 (1989)) may also be prepared. Such recombinant antibodies may be further modified, such as by modification of complementarity determining regions to increase or alter affinity, or "humanizing" such antibodies. Such antibodies may be incorporated into a kit for diagnostic purposes, for example. A diagnostic kit may be employed to determine the location and/or amount of OB receptor of an individual. Diagnostic kits may also be used to determine if an individual has receptors which bind OB protein, or those which, to varying degrees, have reduced binding capacity or ability. As stated *infra*, such antibodies may be prepared using immunogenic portions of an OB receptor protein. Such selective binding molecules may themselves be alternatives to OB protein, and may be formulated for pharmaceutical composition.

Such proteins and/or nucleic acids may be used for tissue distribution assays (for example, as provided in the working example below) or for other assays to determine the location of OB receptor.

The present OB receptor protein family may be used in methods to obtain OB protein analogs, mimetics or small molecules. One would simply prepare a desired OB receptor protein, particularly one with capability of binding to native OB protein, and assay the test molecule, which may be labelled with a detectable label substance, for ability to bind to such receptor. Other parameters, such as affinity, and location of binding, may also be ascertained by methods available to those skilled in the art. For example, one could use portions of the present OB receptors, particularly portions in

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the extracellular domain which are necessary for ligand binding, to determine the location of such binding. One could prepare OB receptors which have various truncations or deletions of regions of the extracellular domain which could be used to determine the location of test molecule binding. One could use an OB receptor known to be defective in native OB binding, such as potentially one from an individual having such defective receptors, and use this as the basis for ascertaining OB protein which would be effective to result in desired biological activity (i.e., weight loss, reduction in blood dyslipidemias or lowering of cholesterol levels, reduction in incidence or severity of diabetes). Other uses include solely cosmetic uses for alteration of body appearance, particularly the removal of fat.

The present OB receptor protein or nucleic acids may also be useful to identify substances which "up-regulate" OB protein or receptor. For instance, the temporal expression of OB receptor in vivo may be useful to determine if an administered substance causes an increase or decrease in OB receptor. One may conclude that an increase in OB receptor expression results in modulation of weight or lipid metabolism.

The divergence in the C-terminus may represent OB receptors with different signal transduction abilities. Therefore the different receptor family members may be used for different assays, depending on the type of signal transduction observed. It is thought that at least a portion of the intracellular domain is necessary for signal transduction (see supra).

The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

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EXAMPLE 1: IDENTIFICATION OF HUMAN OB RECEPTOR PROTEIN

Human OB receptor protein DNA was identified  
5 in a human liver cDNA library in two steps. The first  
step used two primers in polymerase chain reaction (PCR)  
to amplify a selected 300 base pair region from the  
human liver cDNA library. The second step used the PCR  
10 fragment as a probe to screen the human liver cDNA  
library. Thirteen clones were obtained, but these were  
incomplete at the 5' end. A procedure was performed to  
complete the 5' end to make complete clones. Twelve  
clones were sequenced. These twelve clones were  
15 identified as either "A", "B" or "C" as denoted by the  
C-terminus of the predicted amino acid sequence.

Polymerase Chain Reaction.

The original PCR primer was based on the 5'  
end and the 3' end of a 416 base pair sequence having  
20 GenBank Database Accession No. T73849. This sequence  
was selected on the basis of a known motif present in  
cytokine receptors, "WSXWS".

The 5' primer had the sequence 73-96 of the  
416 bp sequence. The 3' primer had the sequence 337-360  
25 of the 416 bp sequence.

These primers were used to probe a human cDNA  
liver library (Stratagene). Standard methods were used.

This resulted in a PCR fragment having the  
sequence 73-360 of the 416 bp fragment.  
30

Hybridization.

The 300 bp PCR fragment was used to probe a  
human liver cDNA library (Stratagene) using standard  
methods. This second hybridization resulted in 13  
35 positive clones. These were partial clones, incomplete  
at the 5' end.

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Completion of the 5' end.

Rapid Amplification of cDNA End ("RACE", kit, GIBCO/BRL) was used to obtain the full length clones.

5

Sequencing results.

Sequencing revealed the three types of OB receptor DNAs. Of the thirteen clones, 4 clones were the "A" type (Seq. ID Nos. 1 and 2); 1 clone was the "B" type (Seq. ID Nos. 3 and 4) and 4 clones were of the "C" type (Seq. ID Nos. 5 and 6).

As can be seen from the Sequence Identifications (below), OB receptor A is 896 amino acids long, "B" is 904 amino acids long, and "C" is 958 amino acids long. These different OB receptors are identical at amino acid positions 1-891, and diverge almost completely beginning at position 892. The leader sequence is postulated to be, by hydrophobicity analysis, amino acids 1-21(M-A), 1-22(M-F) or 1-28(M-I), with the mature protein beginning at positions 22(F), 23(N) or 29(T). Based on hydrophobicity analysis, the leader sequence is most likely to be at positions 1-21(M through A). Chinese Hamster Ovary Cell ("CHO") cell production of the secreted form of OB receptor protein also produced a protein having amino acid number 22 as the first amino acid of the mature protein. The transmembrane region is likely to begin at either position 840 (A) or 842(L) through position 862(I), 863(S) or 864(H). For OB receptor type "A", the last amino acid is located at position 896 and is a lysine (L). For OB receptor type "B", the last amino acid is located at position 904 and is a glutamine (Q). For OB receptor type "C", the last amino acid is located at position 958 and is glutamic acid (E).

35

For OB receptor protein type "C", the C-terminal region possesses high homology to a known human

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transposable element. From nucleotide 2737 through 2947 of the present human OB receptor protein type "C", there is a 98.1% homology with a 211 base section of a human retrotransposable element described in Ono et al., Nucl. Acids Res. 15: 8725-8737 (1987) (bases 520 through 731, SINE-R11, GENBANK accession no. x07417).

#### EXAMPLE 2: TISSUE DISTRIBUTION

Tissue distribution was ascertained using two methods. The first method involved using the entire type "A" OB receptor. The second method involved using probes which are specific to the C-terminal region of the protein. Since these C terminal regions are divergent, the second method detected the tissue distribution of the different members of the OB receptor family.

The first method used a Northern Blot kit (Clontech), using the entire type A OB receptor DNA as a probe. The second method used PCR with primers specific to the nucleic acids encoding the divergent C terminus of the three types. Standard methods were used.

Table 2 shows the results for the Northern Blot and the PCR methods. The "+" indicates the investigator's subjective determination of the strength of signal. For the Northern Blot analysis, a triple "+++" indicates that a result (a dark "band" on the X-ray film) was seen upon overnight exposure of the film. A double "++" indicates that bands were seen at two weeks of exposure. A single "+" indicates that the bands were seen after three weeks of exposure. In addition, using this method, two molecular weights were observed, one at 4 Kb and one at 6.2 Kb. Although distribution was ubiquitous, the strongest signals were seen for ovary, heart and liver. For the PCR analysis, OB receptor "A" was seen in all tissue types tested (prostate, ovary, small intestine, heart, lung, liver

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and skeletal muscle), type "B" was seen only in lung and liver, and type "C" was seen in ovary, heart, lung and liver.

5

Table 2

Tissue Distribution of the Novel OB Receptor

	Northern Blot		PCR		
	4 Kb	6.2 Kb	A	B	C
Spleen	-	+			
Thymus	-	+			
Prostate	-	+	+	-	-
Testis	-	+			
Ovary	-	+++	+	-	+
Small Intestine	-	++	+	-	-
Colon	-	-			
Peripheral blood Leukocyte	-	-			
Heart	-	+++	+	-	+
Brain	-	-			
Placenta	-	+			
Lung	+	++	+	+	+
Liver	+++	+++	+	+	+
Skeletal Muscle	-	++	+	-	-
Kidney	-	++			
Pancreas	-	+			

10

EXAMPLE 3: IDENTIFICATION OF HUMAN OB RECEPTOR GENOMIC DNA AND CHROMOSOME LOCALIZATION; IDENTIFICATION OF HUMAN OB RECEPTOR "D"

15

The full length human OB receptor genomic DNA was also prepared. OB receptor "A" cDNA, in its entirety, was used as a probe against a human genomic DNA library, using materials and methods from a commercially available kit (Genome Systems, using a human genomic library in a P1 vector). A single

20



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positive clone was detected. There are introns located at (with respect to OB receptor "A" DNA) base pair number: 559, 1059, 1350, 1667, 1817, 1937, 2060, 2277, 2460, 2662, and 2738.

5           The human OB receptor gene was localized to human chromosome 1P31 by FISH analysis (Genome Systems). Human chromosome 1 is thought to correspond to mouse chromosome 4C7, which is presumed to be the location of the *db* locus.

10           A further chromosomal sequence was isolated. This chromosomal DNA sequence was isolated from a human genomic library as described above. This chromosomal sequence encodes what is here denominated human OB receptor "D", and the encoded amino acid sequence is set  
15   forth in SEQ. ID No. 7. A cDNA encoding this amino acid sequence is set forth in SEQ. ID No. 8. The chromosomal DNA intron/exon junction map is set forth as SEQ. ID No. 9.

          As with forms "A", "B", and "C", for the  
20   present form "D" OB receptor protein, the first amino acid of the mature protein is likely (using hydrophobicity analysis) to begin at position 22 (F), 23 (N) or 29 (T). The last amino acid of the protein is at position 1165 and is a valine residue. As with the  
25   other forms, the extracellular domain extends from position 22 (F), 23 (N) or 29 (T) to position 839 (D) or 841 (G). The transmembrane domain appears to begin at position 840 (A) or 842 (L). The end of the transmembrane domain appears to be located at position  
30   862 (I), 863 (S) or 864 (H). The C-terminal region, beyond the transmembrane region, is likely to be involved in signal transduction, and is located at position 863 (S), 864 (H) or 865 (Q) through position 1165 (V).

35           The present OB receptor form "D" is identical to that published by Tartaglia et al, Cell 83: 1263-1271

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(December 29, 1995) with the exception of a single amino acid change at amino acid position 976 (nucleotide codon beginning at position 3022). The present type "D" amino acid at position 976 is aspartic acid, and the published amino acid corresponding to the same position is alanine. This is a non-conservative substitution, see infra, and since the location of the substitution is within a region thought important for signal transduction, this change could affect the function of the molecule.

#### EXAMPLE 4: PREPARATION OF SOLUBLE OB RECEPTOR

Three forms of soluble human OB receptor have been prepared:

1. Leader + Extracellular Domain (Seq. ID Nos. 10 and 11): A recombinant form of the soluble human OB receptor was prepared. This form encompasses, in the immature protein, the leader sequence and the extracellular domain (amino acids 1-839). The mature protein would have the leader sequence deleted, and the first amino acid of the mature recombinant soluble human OB receptor would be 22 (F), 23 (N) or 29 (T). This protein was expressed as described below.
2. Leader + Extracellular Domain + C-terminal FLAG (Seq. ID No. 12): A second form of the recombinant soluble human OB receptor was also prepared. This form had a "FLAG" tag located at the "C" terminus of the protein. The "FLAG" peptide is a useful research tool as it allows one to follow the protein using an antibody which recognizes the "FLAG" peptide. Such reagents are commercially available (IBI, New Haven, CT). This protein was expressed as described below.
3. Native Splice Variant (Seq. ID Nos. 13 and 14): This form is believed to be the recombinant form of a naturally occurring secreted,

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soluble human OB receptor. This form has most of the amino acids found in the extracellular domain (amino acids 22-798), and a unique 6 amino acid sequence at the carboxyl terminus. Beginning at amino acid position 799 of Seq. ID No. 13, the amino acid sequence of this native splice variant human OB receptor protein is "G K F T I L."

EXAMPLE 5: PREPARATION OF EXPRESSION VECTORS

10

Recombinant human OB receptor expression vectors have been prepared for expression in mammalian cells. As indicated above, expression may also be in non-mammalian cells, such as bacterial cells. The type "A" cDNA (Seq. ID No. 2) was placed into a commercially available mammalian vector (pCEP4, Invitrogen) for expression in mammalian cells, including the commercially available human embryonic kidney cell line, "293".

Recombinant human OB receptor expression vectors have been prepared for expression of recombinant soluble OB receptor, consisting of the leader sequence and the extracellular domain (Seq. ID Nos. 10 and 11), using the same system as above (the commercially available mammalian vector pCEP4, and "293" cells). This recombinant soluble human OB receptor was also expressed in CHO cells in a similar way.

The "FLAG-tagged" form (Seq. ID No. 12) of the recombinant soluble human OB receptor, and the "D" form (Seq. ID No. 7) were also expressed in "293" cells in a similar fashion as above.

Detection of desired protein was accomplished using BIACORE (Pharmacia) analysis. This analysis is analogous to that described in Bartley et al., Nature 368: 558-560 (1994).

Essentially, the BIACORE machine measures affinity interactions between two proteins. In this

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case, the OB protein was immobilized on the machine, and conditioned media from cell lines expressing the OB receptor was added to the machine. Any receptor protein present in the conditioned media bound to the OB protein surface. The BIACORE machine gave a read-out indicating that receptor protein was being expressed. For recombinant soluble receptor (Seq. ID No. 10) expression in "293" cells, the read-out was 191.0 relative to a baseline readout of 0. For recombinant soluble receptor (Seq. ID No. 10) expression in CHO cells, the read-out was 150.9 relative to a baseline readout of 0. For recombinant soluble receptor with a C-terminal FLAG-tag (Seq. ID. No. 12), the read-out was 172.0 relative to a baseline of 0.

For expression in bacterial cells, one would typically eliminate that portion encoding the leader sequence (e.g., potentially amino acids 1-21, 1-22 or 1-28). One may add an additional methionyl at the N-terminus for bacterial expression. Additionally, one may substitute the native leader sequence with a different leader sequence, or other sequence for cleavage for ease of expression.

#### EXAMPLE 6: DEMONSTRATION OF SIGNAL TRANSDUCTION

25

This example demonstrates that the "D" form is active to produce a signal within a cell, whereas in the same cell type, the "A" form does not. The signal transduction assay was performed by the use of "293" cells transiently expressing either the "A" or the "D" form (see above for preparation of the "293" expression clones). Phosphorylation of molecules predicted to be involved in signal transduction within the cell was examined upon OB protein binding to the OB receptor protein tested. The results demonstrate that upon binding of OB protein to the extracellular domain, the

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"D" form of the present OB protein receptor transduces a signal sufficient to initiate phosphorylation of signalling molecules.

## 5 Methods

1. OB receptor molecules. As indicated above, the "A" form (Seq. ID No. 1) and the "D" form (Seq. ID. No. 7) were studied.

2. Expression system. The pCEP 4 system (as  
10 described above) having inserted DNA encoding the "A" form (Seq. ID No. 2) or the "D" form (Seq. ID No. 8) was used to transfect "293" cells. These cells did not allow for the pCEP4 vector to integrate into the genome, so such expression was transient. Non-recombinant  
15 (mock-transfected) cells were also prepared as controls.

3. Detection of phosphorylation. Mock transfected cells and cells expressing the "A" form or the "D" form were analyzed. Prior to treatment the cells were serum-starved by incubation in media with  
20 0.5% serum for 16 hours prior to the treatments. The cells were treated with the OB protein (10 mg/ml) for 15 minutes at 37°C, after which the cells were lysed in modified NP40 buffer (50 mM Tris, pH 8.0, 150 mM sodium chloride, 1% NP40, 10 mg/ml aprotinin, 5mM EDTA, 200 mM  
25 sodium orthovanadate). Phosphotyrosine containing proteins were immunoprecipitated (Anti-phosphotyrosine antibody 4G10, UBI, Lake Placid, NY), and separated by SDS polyacrylamide gel electrophoresis. After electrophoresis and electroblotting to membranes the  
30 immunoprecipitates were probed with antibodies to various signal transduction molecules. Antibodies to STATs, JAKs and ERKs were purchased from Santa Cruz Biotechnology Inc. Immune complexes were detected by horseradish peroxidase conjugated secondary reagents  
35 using chemiluminescence as described by the manufacturer (ECL, Amersham). As a positive control, 32D cells were

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treated with IL-3, which is known to activate by tyrosine phosphorylation most of the molecules being analyzed.

4. Results. Results are presented in Table 3, below. As can be seen, only the "D" form was able to respond to either mouse or human OB protein as detected by phosphorylation of JAK and STAT molecules. A "+" designation indicates signal was detected, a "-" designation means that no signal was observed.

10

TABLE 3

Signal /AB‡	293 Alone	293/D hrOB*	293/D mrOB**	293/A hrOB#	293/A mrOB##	32D IL-3
STAT1	-	+				
STAT3	-	+	+	-	-	+
STAT5	-	+	+			+
JAK1	-	+	+	-	-	+
JAK2	-	+	+	-	-	+
JAK3	-	-	-			-
TYK2	-	+	+			-
ERKs 1,2	-	-	-	-	-	+

‡ Antibody detection target

- \* 293 cells expressing receptor form "D", treated with recombinant human OB

\*\* 293 cells expressing receptor form "D" treated with recombinant murine OB

# 293 cells expressing receptor form "A" treated with recombinant human OB

- ## 293 cells expressing receptor form "A" treated with recombinant murine OB

The "D" form is capable of initiating signalling through the JAK/STAT pathways in 293 cells, whereas the "A" form cannot.

EXAMPLE 7: USE OF SOLUBLE OB RECEPTOR AS A THERAPEUTIC

This example demonstrates that soluble OB  
5 receptor protein acts to protect the activity of OB  
protein. Below, soluble OB receptor and/or OB protein  
was delivered to a mammal via "gene transplant" -- that  
is, via bone marrow cells engineered to express the  
desired DNAs. When soluble OB receptor combined with OB  
10 protein was delivered, the animals lost more weight than  
delivery of OB protein alone. This demonstrates the  
protective activity of OB receptor protein.

While not wishing to be bound by theory, one  
explanation of the mode of action is that soluble OB  
15 receptor protein acts to protect the OB protein in serum  
from agents or conditions which could diminish its  
activity. The protective action appears to increase  
circulating half-life of the protein. As such, the  
present example demonstrates that OB receptor either  
20 alone, or administered as a complex with OB protein (or  
analog or derivative thereof) could act as a therapeutic  
agent.

Materials and methods:

25 1. Preparation of recombinant ob retroviral  
vector Packaging Cells.

Use of murine ob cDNA. Full length wild-type  
murine ob cDNA was amplified by the PCR using synthetic  
oligonucleotides designed from the published sequence  
30 Zhang et al., Nature 372: 425-432 (1994). Linkers (An Eco  
RI linker and a Bgl II linker) were used to facilitate  
subcloning.

Use of soluble recombinant human OB receptor  
cDNA. Methods similar to those above were used. A  
35 construct containing the recombinant human soluble  
receptor of Seq. ID No. 10 was used, and modified with

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linkers to facilitate cloning (i.e., the addition of a Bgl II restriction endonuclease recognition site).

Placement of desired cDNA into vector. PCR products were digested with *Eco*RI and *Bgl*II and cloned  
5 into similarly-digested parental vector (pMSCV2.1) under the transcriptional control of the viral LTR promoter. The parental MSCV vector (supplied by R. Hawley, University of Toronto, Canada) was derived from MESV (murine embryonic stem cell virus) and contains a  
10 neomycin phosphotransferase resistance (*neo*<sup>r</sup>) gene driven by an internal mouse phosphoglycerate kinase (PGK) promoter, as described. Hawley, et al, J. Exp. Med. 176: 1149 -1163 (1992). The parental plasmid pMSCV2.1 and pMSCV-OB were independently electroporated  
15 into the GP+E-86 packaging cell line (supplied by Dr. A. Bank, Columbia University, NY) Markowitz et al., J. Virol. 62:1120-1124 (1988). Transient supernatants were harvested from electroporated populations and used to infect tunicamycin treated parental GP+E-86 cells.  
20 Tunicamycin treatment relieves the block to superinfection of the parental packaging cells. G418 (0.78 mg/mL, 67% active, GIBCO Laboratories, Life Technologies, Inc., Grand Island, NY) resistant clones were selected from each infected population and titered  
25 by infection of NIH3T3 cells. Clones with the highest G418 resistant titer were expanded and frozen as aliquots. Each bone marrow infection and transplantation experiment used aliquots from the same passage of frozen viral packaging cells. Both the  
30 parental and ob packaging cell lines were tested for the presence of, and found to be free from, replication competent virus using a sensitive marker rescue assay. Moore, et al., (1993) in: Gene Targeting: A Practical Approach, Joyner, Ed. (Oxford University Press, New  
35 York, NY).



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## 2. Production of Retroviral Supernatants.

Recombinant virus-producing packaging cell lines were grown in 175cm<sup>2</sup> tissue culture flasks in Iscove's Modified Dulbecco's Medium (IMDM) (GIBCO), 10% (v/v) FBS, at 37°C. Sub-confluent (approximately 60%) monolayers of cells were fed with fresh medium 24h prior to harvest of virus-containing supernatants. Viral supernatants were removed from packaging cell lines by aspiration, sterile filtered (0.45µm) and added directly to bone marrow cultures. Fresh aliquots of frozen packaging cell lines were thawed for use in each experiment.

## 3. Bone Marrow Infection and Transplantation.

Eight to 12-week old female C57BL/6J (+/+) or (ob/ob) mice were used as bone marrow donors and recipients. All mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and housed under specific pathogen-free conditions in a vivarium in accordance with governmental regulations and institutional guidelines.

Bone marrow cells were harvested from femurs and tibias of donor mice 4 days post 5-fluorouracil (5-FU, Sigma Chemical Co., St. Louis, MO) treatment (150 mg/kg i.v.). Bone marrow cells ( $6 \times 10^5$ /mL) were incubated in 150mm tissue culture dishes (30mL/dish) containing fresh viral supernatant (as described above), 15% FBS, 6 mg/mL polybrene (Sigma), 0.1% bovine serum albumin (BSA, Fraction V, Sigma), 2.5 ng/mL recombinant mouse IL-3 (rmIL-3), 100 ng/mL each of recombinant human IL-6 (rhIL-6), recombinant human IL-11 (rhIL-11), and recombinant rat SCF (rrSCF). All growth factors were produced by Amgen, Inc. (Thousand Oaks, CA). Culture media were replaced daily for 3 days with fresh virus-containing supernatant and growth factors.

At the end of the infection period, total non-adherent and adherent cells were washed and resuspended in 1% BSA-saline and transplanted into g-irradiated (12

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Gy, Cs<sup>137</sup>) mice. Each animal was transplanted with  $2.5 \times 10^6$  syngeneic cells. There were approximately 10 animals per cohort.

4. Analysis of OB protein expression in  
5 transfected cells and transplanted animals. For  
transfected bone marrow cells, Western analysis was  
performed. Vector packaging cell supernatant was  
resolved by SDS-PAGE (16% acrylamide), then transferred  
to Hybond-ECL (Amersham, Arlington Heights, IL). The  
10 filter was incubated with affinity-purified rabbit a-  
mouse OB protein polyclonal antibody (1mg/mL) in T-TBS  
buffer (20mM Tris-chloride, pH7.6, 137mM NaCl, 0.1%  
Tween20) at room temperature for 45 min. Horseradish  
peroxidase (HRP)-conjugated donkey a-rabbit IgG  
15 (Amersham) was diluted in T-TBS (1:2500) and incubated  
with the filter at room temperature for 45 min.  
Enhanced chemiluminescence (ECL, Amersham) detection was  
performed as recommended by the manufacturer.

- For transplanted animals, serum was analyzed.  
20 Animals were bled retroorbitally, under isofluorane  
anesthesia. Serum from transplanted *ob/ob* animals was  
resolved by SDS-PAGE (4-20% acrylamide) under non-  
reducing and reducing conditions, then transferred to  
Trans-Blot (Bio-Rad Laboratories, Hercules, CA)  
25 membranes. The membranes were incubated for 2 hours at  
room temperature with HRP-conjugated rabbit a-mouse OB  
protein antibody (0.125mg/mL) in T-TBS buffer containing  
5% fetal bovine serum and 1% bovine serum albumin.  
Bound OB protein was detected by ECL (Amersham),  
30 performed as recommended by the manufacturer.

- For quantitation of soluble OB protein levels,  
serum from transplanted animals was subjected to ELISA  
analysis. Briefly, affinity-purified rabbit a-OB  
protein polyclonal antibody was coated onto 96-well  
35 plates. Standards (purified recombinant OB protein

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monomer, Pelleymounter et al., Science 269: 540-543 (1995) and experimental samples were added, and the plates were incubated at room temperature. The plates were washed twice and affinity-purified rabbit a-OB protein antibody conjugated to horseradish peroxidase was added. Following incubation at room temperature, the plates were washed four times with TNE-Tween20. TMB/peroxide substrate was added and the color reaction was read at 450nm in a Molecular Devices plate reader. OB protein concentrations in sera were estimated by comparison to a standard curve prepared from internal standards. OB protein levels were reliably measured in samples containing >160 pg/mL.

5. Body Weight and Food Intake. Mice were offered pelletized rodent chow (PMI Feeds, Inc., St. Louis, MO) ad libitum. The body weight of individual animals was measured daily for the first two months of analysis, and weekly thereafter. Food consumption was measured daily on selected groups of individually-housed animals.

### Results

Results are presented in Tables 4 and 5 below. Administration of OB protein receptor increased the effectiveness of OB protein. This may have been accomplished via an increased circulation time of OB protein in the presence of OB protein receptor.

As can be seen in the Table, animals administered a combination of OB protein and OB protein receptor (via genetic therapy) had a greater weight loss after 28 days than either composition alone. The Table presents the results of two experiments ("\_\_\_/\_\_\_"). As can be seen, use of the OB protein alone at day 40 resulted in animals with 87.5% and 72.2% of the starting weight. Using OB receptor in combination with OB protein, however, resulted in animals with 68% and

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53.6% of the starting weight. Use of the receptor alone appeared to have little effect, if any.

TABLE 4

5

Treatment	Weight (g) decrease at day 28 (ave)	% starting weight (ave) day 28	% starting weight (ave) day 40
OB alone*	6.3/12.7	87.9/75.3	87.5/72.2
Receptor** alone	[1.4]/[0.3]	103/100.6	104.2/101.7
OB + Receptor***	12.6/16.8	76.3/67.5	68/53.6

\* 50% bone marrow cells transfected with OB protein cDNA as described above, and 50% bone marrow cells without genetic alteration

10 \*\* 50% bone marrow cells transfected with OB receptor protein cDNA as described above, and 50% bone marrow cells without genetic alteration

15 \*\*\* 50% bone marrow cells transfected with OB protein cDNA as described above, and 50% bone marrow cells transfected with OB receptor protein cDNA as described above.

20 Table 5, below, contains results of the OB levels found in the serum from animals administered OB protein alone, or administered OB protein in combination with OB protein receptor (via the "gene therapy" method of this example). The data reflect nanograms of OB protein per milliliter of serum, plus or minus the standard error of the mean.

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TABLE 5

Treatment	Experiment #1†	Experiment #2‡
OB alone*	2.93 +/- 0.77	9.74 +/- 1.02
Receptor** alone	0.08 +/- 0.05	0.12 +/- 0.07
OB + Receptor***	12.11 +/- 1.90	15.18 +/- 2.52

\* 50% bone marrow cells transfected with OB protein  
5 cDNA as described above, and 50% bone marrow cells  
without genetic alteration

\*\* 50% bone marrow cells transfected with OB receptor  
protein cDNA as described above, and 50% bone marrow  
cells without genetic alteration

10 \*\*\* 50% bone marrow cells transfected with OB protein  
cDNA as described above, and 50% bone marrow cells  
transfected with OB receptor protein cDNA as described  
above.

† Experiment #1 was conducted as described above,  
15 with OB protein serum levels measured after 38 days.

‡ Experiment #2 was also conducted as described  
above, with OB protein serum levels measured after 24  
days.

The data demonstrate the protective effects of  
20 OB receptor. As can be seen, in the presence of OB  
receptor, OB protein has a higher accumulation in the  
serum. The degree of accumulation is observed to  
increase inversely with the levels of OB protein in the  
serum. In Experiment #1 (with a base OB protein level  
25 of about 2.93 ng/ml), the OB protein serum level  
increased about 400% with the addition of receptor,  
where in Experiment #2 (with a base of about 9.74), the  
OB protein serum level increased by about 25%.

OB receptor administered either alone or in  
30 association with OB protein (or analogs or derivatives

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thereof) may serve to increase the circulation time of OB protein, and therefore enhance the therapeutic efficacy of either exogenous or endogenous OB protein.

5    EXAMPLE 8: PREPARATION OF SELECTIVE BINDING MOLECULES

Animals were immunized for the preparation of polyclonal antibodies using the following peptides (with respect to the numbering of the amino acids for OB receptor A, Seq. ID No. 1): 54-64; 91-100; 310-325;  
10    397-406; 482-496; 874-885; and, with respect to amino acids of OB receptor "C" (Seq. ID No. 5), 910-929. Some of the polyclonal antibodies prepared (in rabbits) were tested for ability to bind to recombinant human OB receptor protein. The polyclonal antibody prepared  
15    against amino acids 54-64 was found to have the highest affinity for recombinant human OB receptor protein. The polyclonal antibody prepared against amino acids 397-406 was also found to bind to recombinant human OB receptor protein. The polyclonal antibody prepared against amino  
20    acids 91-100 was found to slightly bind to recombinant human OB receptor protein. The polyclonal antibody prepared against amino acids 874-885 was found not to bind to recombinant human OB receptor protein.

An additional study was performed which  
25    demonstrates the expression and purification of the extracellular domain of the OB receptor protein in CHO cells, and antibodies which recognize this OB protein receptor extracellular domain.

The extracellular domain of the human OB  
30    receptor protein was expressed as a secreted, soluble protein in CHO cells as previously described supra. Individual cell lines were isolated and grown in increasing amounts of methotrexate to increase selection/expression of the recombinant receptor protein  
35    (100, 200 or 500 micrograms methotrexate per ml of media). Conditioned media from the CHO cell lines was

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collected, and the proteins in the conditioned media were fractionated by SDS-PAGE. The OB receptor extracellular domain migrated as a broad band with an apparent size range of about 140 kDa to about 200 kDa.

5 The OB receptor protein extracellular domain was detected by Western Blot analysis using polyclonal antibodies prepared against a portion of the extracellular domain of the OB receptor protein. The unfolded, bacterially expressed protein was used as an antigen to  
10 generate antisera in rabbits. The identified OB receptor extracellular domain was purified by affinity chromatography. The purified protein was sequenced at the amino terminus to confirm that it was the OB  
15 receptor and also to determine the start of the mature protein (after signal peptide cleavage) as expressed in CHO cells. It was found that amino acid no. 22 (according to the amino acid sequence numbering of Seq. ID No. 1, *infra*), was the first amino acid of the mature protein as expressed in CHO cells.

20 Other immunogenic peptides may be used. Polyclonal, monospecific polyclonal, monoclonal, antibody fragments, and recombinant antibodies may be prepared using methods available to those skilled in the art.

25 One may further use recombinant techniques or peptide synthesis methods to alter the character of such selective binding molecules. This may be accomplished by preparing recombinant antibodies having altered complementarity determining regions (sometimes referred  
30 to in the art as "CDR's") to, for example "humanize" the antibodies by using human F<sub>C</sub> (constant) regions. Other types of recombinant antibodies, for example, those having CDR's altered to enhance affinity or selectivity to one or more members of the OB receptor family, may be  
35 prepared and used using methods available to those

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skilled in the art. See Winter et al., Nature 349: 293-299 (1991).

The present OB receptor protein may be used as an assay to screen for desired selective binding molecules. Such assay may be based on binding capability, or biological activity, or, other means of detecting signal transduction. For example, if one were to prepare a series of modified antibodies, one could test them for affinity (i.e, binding strength) against the target OB receptor.

The selective binding molecules may be useful for diagnostic purposes, such as tissue distribution analysis, or to diagnose the relative affinity of an individual's OB receptors for such selective binding molecule to determine the functionality of an individual's OB receptor during a course of therapy. Selective binding molecules may be alternative therapeutic or cosmetic products to OB protein.

#### 20 EXAMPLE 9: GENE THERAPY

One may deliver the present OB receptor protein via gene therapy, as described infra.

One may envision, using materials and methods available to those skilled in the art and provided herein, using T-cells as an agent carrying DNA expressing OB receptor for gene therapy. An individual would have T-cells selected using CD34+ selection and a magnetic microparticles selection device. Such cells would be transfected with the desired DNA, or the regulation of the desired coding region may be altered using homologous recombination or other in situ techniques. The transduced cells could be selected empirically, using means to detect the desired protein, or a marker may be included which permits indirect detection (i.e., a selectable marker as is known in the



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art). Optionally, such cells could be expanded, for example, using one or more growth factors such as SCF or an interleukin, and such cells could be stored for future use. In such a way, the procedure would only  
5 have to be accomplished once or infrequently in an individual's lifetime, for later transfer into the individual. The cells would be re-planted into the individual, and the individual would be monitored for desired therapeutic effect, such as weight  
10 loss/maintenance of weight, diabetes recurrence, blood lipid levels, or other conditions.

#### Illustrative Nucleic Acid and Amino Acid Sequences

The below amino acid and DNA sequences are  
15 those to which reference has been made. An asterick("\*\*\*") indicates the position of a stop codon.

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Human OB Receptor "A" Amino Acid Sequence (Seq. ID No. 1 (Amino Acid, single letter abbreviation)):

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP  
5 51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10 151 LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
251 GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP  
15 301 GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSE  
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK  
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTGMTCRWS  
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
25 551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701 FTFWLTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNED GEIKWLRISX SVKKYYIHDH  
35 801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII  
851 SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KRTDIL\*SLI  
40 901 MITTDEPNVP TSQQSIEY\*K IFTF\*RRGAN LKKIQLNF\*E LTYGGLC\*FR  
951 T\*NRCVNLGS KCRFESSLDV \*L

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Human OB Receptor "A" DNA Sequence (Seq. ID No. 2 (DNA)):

```

1      CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA
5  51    CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA
      101    TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA
      151    CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
10  201    TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
      251    ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15  301    TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
      351    GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
      401    TTCAACAGTA AATTCTTTAG TTTTTCACAA AATAGATGCA AACTGGAACA
20  451    TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG
      501    TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25  551    ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAAG
      601    GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTCATGA ATGTTGTGAA
      651    TGTCTTGTGC CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG
30  701    TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
      751    TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35  801    GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
      851    GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
      901    CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
40  951    GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
      1001   ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45  1051   CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG
      1101   TCTAATGTTT CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC
      1151   CTCAAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA
50  1201   GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT
      1251   CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG

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1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG  
1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG  
5 1401 ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT  
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA  
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT  
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG  
1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG  
15 1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA  
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT  
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGAA  
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT  
1851 GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG  
25 1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG  
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT  
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT  
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT  
2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG  
35 2151 GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG CACATACTGT  
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT  
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT  
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC  
2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAG AATCTTAATG  
45 2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTATCTGT TAAGAAGTAT  
2451 TATATCCATG ATCATTTTAT CCCCATGAG AAGTACCACT TCAGTCTTTA  
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA  
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT

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2601 GTGCCAGTAA TTATTCCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT  
2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA  
5 2701 AGAATTGTTT CTGGGCACAA GGACTTAATT TTCAGAAGAG AACGGACATT  
2751 CTTTGAAGTC TAATCATGAT CACTACAGAT GAACCCAATG TGCCAACTTC  
2801 CCAACAGTCT ATAGAGTATT AGAAGATTTT TACATTTTGA AGAAGGGGAG  
10 2851 CAAATCTAAA AAAAATTCAG TTGAACTTCT GAGAGTTAAC ATATGGTGGA  
2901 TTATGTTGAT TTAGAACTTA AAATAGATGT GTAAATTTGG GTTCAAAATG  
15 2951 TAGATTTGAG TCCAGTTTGG ATGTGTGATT AATTTTCAAA TCATCTAAAG  
3001 TTTAAAAGTA GTATTCATGA TTTCTGGCTT TTGATTTGCC ATATTCCTGG  
3051 TCATAAAACA TTAAGAAAAT TATGGCTGTT GCTGTCATTA CATATCTATT  
20 3101 AAATGTCATC AAATATGTAG TAGACAATTT TGTAATTAGG TGAACCTAA  
3151 AACTGCAACA TCTGACAAAT TGCTTTAAAA ATACAATGAT TAT

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Human OB Receptor "B" Amino Acid Sequence (Seq. ID No. 3 (Amino Acid)):

5    1    MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP  
51    AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101   LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10   151   LFRNINYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201   PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
15   251   GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP  
301   GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSE  
351   HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK  
20   401   PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS  
451   TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
25   501   QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
551   IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601   PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30   651   GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701   FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
35   751   SSCVIVSWIL SPSDYKLMYF IIEWKNLNED GEIKWLRISS SVKKYYIHDH  
801   FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII  
851   SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KKRLSIFLSS  
40   901   IQHQ\*HVVLF FWSLKQFQKI SVLIHHGKIK MR\*COQLWSL YFQQQILKRV  
951   LFVLVTSSTV LTSLRLRVLR \*PMRTKARDN PLLNTPR\*SA TLNQVKLVK  
45

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Human OB Receptor "B" DNA Sequence (Seq. ID No. 4 (DNA)):

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1      CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA
5  51    CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA
      101    TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA
      151    CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
10  201    TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
      251    ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15  301    TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
      351    GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
      401    TTCAACAGTA AATTCTTTAG TTTTTCACAA AATAGATGCA AACTGGAACA
20  451    TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG
      501    TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25  551    ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG
      601    GCAGTTTTC A GATGGTTCAC TGCAATTGCA GTGTTCATGA ATGTTGTGAA
      651    TGTCTTGTGC CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG
30  701    TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
      751    TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35  801    GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
      851    GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
      901    CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
40  951    GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
      1001   ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45  1051   CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG
      1101   TCTAATGTTT CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC
      1151   CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA
50  1201   GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT
      1251   CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG

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1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG  
1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG  
5 1401 ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT  
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA  
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT  
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG  
1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG  
15 1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA  
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT  
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGAA  
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT  
1851 GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG  
25 1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG  
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT  
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT  
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT  
2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG  
35 2151 GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG CACATACTGT  
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT  
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT  
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC  
2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAA AATCTTAATG  
45 2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTATCTGT TAAGAAGTAT  
2451 TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT TCAGTCTTTA  
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA  
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT



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2601 GTGCCAGTAA TTATTTCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT  
2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA  
5 2701 AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAA ACGTTTGAGC  
2751 ATCTTTTTAT CAAGCATACA GCATCAGTGA CATGTGGTCC TCTTCTTTTG  
2801 GAGCCTGAAA CAATTTTCAGA AGATATCAGT GTTGATACAT CATGGAAAAA  
10 2851 TAAAGATGAG ATGATGCCAA CAACTGTGGT CTCTCTACTT TCAACAACAG  
2901 ATCTTGAAAA GGGTTCTGTT TGTTTTAGTG ACCAGTTCAA CAGTGTTAAC  
15 2951 TTCTCTGAGG CTGAGGGTAC TGAGGTAACC TATGAGGACG AAAGCCAGAG  
3001 ACAACCCTTT GTTAAATACG CCACGCTGAT CAGCAACTCT AAACCAAGTG  
3051 AAAGTGGTGA AGA

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Human OB Receptor "C" Amino Acid Sequence (Seq. ID No. 5 (Amino Acid)):

5    1    MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP  
51    AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101    LCADNIEGKT FVSTVNSLVE QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10    151    LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201    PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
15    251    GNLKISWSSP PLVPFPLOYQ VKYSENSTTV IREADKIVSA TSLLVDSILP  
301    GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF  
351    HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFNINLNETK  
20    401    PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTGMTCRWS  
451    TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
25    501    QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
551    IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601    PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30    651    GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701    FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
35    751    SSCVIVSWIL SPSDYKLMYF IIEWKNLNEE GEIKWLRISX SVKKYYIHDH  
801    FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII  
851    SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KMLEGSMFVK  
40    901    SHHHSLSIST QGHKHCGRPQ GPLHRKTRDL CSLVYLLTLP PLLSYDPAKS  
951    PSVRNTQE\*S IKKKKKKKLEG

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Human OB Receptor "C" DNA Sequence (Seq. ID No. 6 (DNA)):

```

1      CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA
5
51     CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA
101    TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA
10
151    CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC
201    TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA ATTCGAATGG
251    ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT
15
301    TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA
351    GATAGAAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT
20
401    TTCAACAGTA AATTCTTTAG TTTTTCACAA AATAGATGCA AACTGGAACA
451    TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG
501    TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT
25
551    ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAAG
601    GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA
30
651    TGTCTTGTGC CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG
701    TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG
751    TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG
35
801    GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT
851    GGTACCATTT CCACTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA
40
901    CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA
951    GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG
1001   ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA
45
1051   CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG
1101   TCTAATGTTT CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC
50
1151   CTCAAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAAA
1201   GCCAGTATGA TGTTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTTCAAT

```

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1251 CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG  
1301 CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG  
5 1351 ATGTCAATAT CAATATCTCA TGTGAAACTG ATGGGTACTT AACTAAAATG  
1401 ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT  
1451 GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA  
10 1501 TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT  
1551 TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG  
15 1601 GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG  
1651 TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA  
1701 GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT  
20 1751 CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGAA  
1801 AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAAA ATCAAAATCT  
25 1851 GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG  
1901 CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG  
1951 CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT  
30 2001 TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT  
2051 ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT  
35 2101 ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG  
2151 GGAAATCACA CGAAATTCAC TTTCCTGTGG ACAGAGCAAG CACATACTGT  
2201 TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT  
40 2251 TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACTCAGT  
2301 GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC  
45 2351 CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAA AATCTTAATG  
2401 AAGATGGTGA AATAAAATGG CTTAGAATCT CTTCATCTGT TAAGAAGTAT  
2451 TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT TCAGTCTTTA  
50 2501 CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA  
2551 CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT

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2601 GTGCCAGTAA TTATTTCTC TTCCATCTTA TTGCTTGGAA CATTATTAAT  
5 2651 ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA  
2701 AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAT GCTTGAAGGC  
2751 AGCATGTTCG TTAAGAGTCA TCACCACTCC CTAATCTCAA GTACCCAGGG  
10 2801 ACACAAACAC TGCGGAAGGC CACAGGGTCC TCTGCATAGG AAAACCAGAG  
2851 ACCTTTGTTC ACTTGTTTAT CTGCTGACCC TCCCTCCACT ATTGTCCTAT  
15 2901 GACCCTGCCA AATCCCCCTC TGTGAGAAAC ACCCAAGAAT GATCAATAAA  
2951 AAAAAAAAAA AAAAAACTCG AGGGGG

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Human OB Receptor "D" Amino Acid Sequence (Sequence ID No. 7)

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP  
5 51 AGLSKNTSNS NGHJETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10 151 LFRNINYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
251 GNLKISWSSP PLVPFPLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP  
15 301 GSSYEVQVRG KRLDGPGIWS DWSTPRVETT QDVIYFPPKI LTSVGSNVSF  
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSK VTFFNLNETK  
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTGMTCRWS  
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
25 551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
751 SSCVIVSWIL SPSDYKLMYF IIEWKNLNE DGEIKWLRIS SVKKYYIHDH  
35 801 FIPIEKYQFS LYPIFMEGVG KPKIINSFTQ DDIEKHQSDA GLYVIVPVII  
851 SSSILLLGTL LISHQRMKKL FWEDVPNPKN CSWAQGLNFQ KPETFELFI  
40 901 KHTASVTCGP LLEPETISE DISVDTSWKN KDEMPPTTVV SLLSTTDLEK  
951 GSV CISDQFN SVNFSEAEGT EVTYEDESQR QPFVKYATLI SNSKPSETGE  
1001 EQGLINSSVT KCFSSKNSPL KDSFSSNSWE IEAQAFFILS DQHPNIISPH  
45 1051 LTFSEGLDEL LKLEGNFPEE NNDKKSIIYL GVTSIKKRES GVLLTDKSRV  
1101 SCPFPAPCLF TDIRVLQDSC SHFVENNINL GTSSKKTFAS YMPQFQTCST  
50 1151 QTHKIMENKM CDLTV\*FH\*R NLQICVIMGN IKCNRL\*LWV GERKETRVKF  
1201 ENNCSK\*KKK KKNSRPARPD

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Human OB Receptor "D" Nucleic Acid Sequence (Sequence ID No. 8)

1	GCGGCCGCCA	GTGTGATGGA	TATCTGCAGA	ATTCGGCTTT	CTCTGCCTTC
5	51	GGTCGAGTTG	GACCCCCGGA	TCAAGGTGTA	CTTCTCTGAA
	101	TTGTCAAAAA	TTCTGTGTGG	TTTTGTTACA	TTGGGAATTT
	151	TAAGTGCATT	TAAGTTGTCA	TATCCAATTA	CTCCTTGGAG
10	201	TCTTGCATGC	CACCAAATTC	AACCTATGAC	TACTTCCTTT
	251	GCTCTCAAAG	AATACTTCAA	ATTCGAATGG	ACATTATGAG
15	301	AACCTAAGTT	TAATTCAAGT	GGTACTCACT	TTTCTAAGTT
	351	ACTTTCCACT	GTTGCTTTTC	GAGTGAGCAA	GATAGAAACT
	401	TGCAGACAAC	ATTGAAGGAA	AGACATTTGT	TTCAACAGTA
20	451	TTTTTCAACA	AATAGATGCA	AACTGGAACA	TACAGTGCTG
	501	GACTTAAAAT	TATTCATCTG	TTATGTGGAG	TCATTATTTA
25	551	CAGGAATTAT	AACATAAAGG	TCCATCTTTT	ATATGTTCTG
	601	TAGAAGATTC	ACCTCTGGTT	CCCCAAAAG	GCAGTTTTCA
	651	TGCAATTGCA	GTGTTACGAA	ATGTTGTGAA	TGTCTTGTGC
30	701	AGCCAAACTC	AACGACACTC	TCCTTATGTG	TTTGAAAATC
	751	GAGTAATTTT	CCAGTCACCT	CTAATGTCAG	TTCAGCCCAT
35	801	AAGCCTGATC	CACCATTAGG	TTTGCATATG	GAAATCACAG
	851	TTTAAAGATT	TCTTGGTCCA	GCCCACCATT	GGTACCATTT
	901	ATCAAGTGAA	ATATTCAGAG	AATTCTACAA	CAGTTATCAG
40	951	AAGATTGTCT	CAGCTACATC	CCTGCTAGTA	GACAGTATAC
	1001	TTCGTATGAG	GTTCAGGTGA	GGGGCAAGAG	ACTGGATGGC
45	1051	GGAGTGACTG	GAGTACTCCT	CGTGTCTTTA	CCACACAAGA
	1101	TTTCCACCTA	AAATTCTGAC	AAGTGTTGGG	TCTAATGTTT
	1151	CATCTATAAG	AAGGAAAACA	AGATTGTTCC	CTCAAAGAG
50	1201	GGATGAATTT	AGCTGAGAAA	ATTCCTCAAA	GCCAGTATGA
	1251	GATCATGTTA	GCAAAGTTAC	TTTTTTCAAT	CTGAATGAAA

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1301 AGGAAAGTTT ACCTATGATG CAGTG TACTG CTGCAATGAA CATGAATGCC  
1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA  
5 1401 TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG  
1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA  
10 1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC  
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC  
1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC  
15 1651 TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG  
1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG  
20 1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC  
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG  
1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA  
25 1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC  
1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT  
30 2001 ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA  
2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA  
2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT  
35 2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC  
2201 TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT  
40 2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG  
2301 AGCAAAGTAA ATATCGTGCA GTCAC TCAGT GCTTATCCTT TAAACAGCAG  
2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT  
45 2401 ATTTTATTAT TGAGTGGA AATCTTAATG AAGATGGTGA AATAAAATGG  
2451 CTTAGAATCT CTT CATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT  
50 2501 CCCCAT TGAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG  
2551 TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA



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2601 CACCAGAGTG ATGCAGGTTT ATATGTAATT GTGCCAGTAA TTATTCCTC  
2651 TTCCATCTTA TTGCTTGGAA CATTATTAAT ATCACACCAA AGAATGAAAA  
5 2701 AGCTATTTTG GGAAGATGTT CCGAACCCCA AGAATTGTTC CTGGGCACAA  
2751 GGACTTAATT TTCAGAAGCC AGAAACGTTT GAGCATCTTT TTATCAAGCA  
2801 TACAGCATCA GTGACATGTG GTCCTCTTCT TTTGGAGCCT GAAACAATTT  
10 2851 CAGAAGATAT CAGTGTTGAT ACATCATGGA AAAATAAAGA TGAGATGATG  
2901 CCAACAACCTG TGGTCTCTCT ACTTTCAACA ACAGATCTTG AAAAGGGTTC  
15 2951 TGTTTGTATT AGTGACCAGT TCAACAGTGT TAACTTCTCT GAGGCTGAGG  
3001 GTACTGAGGT AACCTATGAG GACGAAAGCC AGAGACAACC CTTTGTTAAA  
3051 TACGCCACGC TGATCAGCAA CTCTAAACCA AGTGAAACTG GTGAAGAACA  
20 3101 AGGGCTTATA AATAGTTCAG TCACCAAGTG CTTCTCTAGC AAAAATTCTC  
3151 CGTTGAAGGA TTCTTTCTCT AATAGCTCAT GGGAGATAGA GGCCCAGGCA  
25 3201 TTTTTTATAT TATCGGATCA GCATCCCAAC ATAATTTAC CACACCTCAC  
3251 ATTCTCAGAA GGATTGGATG AACTTTTGAA ATTGGAGGGA AATTTCCCTG  
3301 AAGAAAATAA TGATAAAAAG TCTATCTATT ATTTAGGGGT CACCTCAATC  
30 3351 AAAAAGAGAG AGAGTGGTGT GCTTTTGA CTGACAAGTCAA GGGTATCGTG  
3401 CCCATTCCCA GCCCCCTGTT TATTCACGGA CATCAGAGTT CTCCAGGACA  
35 3451 GTTGCTCACA CTTTGTAGAA AATAATATCA ACTTAGGAAC TTCTAGTAAG  
3501 AAGACTTTTG CATCTTACAT GCCTCAATTC CAAACTTGTT CTACTCAGAC  
3551 TCATAAGATC ATGGAAAACA AGATGTGTGA CCTAACTGTG TAATCTAGA

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Human OB Receptor Protein "D" Chromosomal DNA (Seq. ID No. 9)

5				Intron 1	.....taccttttccag	GTG TAC TTC
10	CAT TGG G	gtaagttatttg.....	Intron 2	.....atatacctaacag	AA TTT ATT	Phe Ile
	His Trp Glu					15 16
	12 13 14					
15	CAA ATA G	gtaagcatttagc.....	Intron 3	.....ttttaaattcag	AT GCA AAC	Ala Asn
	Gln Ile Asp					125 126
	122 123 124					
20	TAT GTT CT	gtaagtaccaaa.....	Intron 4	.....ttttcaatatag	G CCT GAA	Pro Glu
	Tyr Val Leu					166 167
	163 164 165					
25	AAT ATG G	gtaagttatgca.....	Intron 5	.....tttttccttaag	TG AAG CCT	Lys Pro
	Asn Met Val					236 237
	233 234 235					
30	ATC AGA GAA	gtaagtatatatt.....	Intron 6	.....aatatttaacag	GCT GAC AAG	Ala Asp Lys
	Ile Arg Glu					284 285 286
	281 282 283					
35	ACA CAA G	gtaggttatgta.....	Intron 7	.....ccctcattacag	AT GTC ATA	Val Ile
	Thr Gln Asp					333 334
	330 331 332					
40	GTG ATT G	gtaagaaaacag.....	Intron 8	.....tgtttcaaatag	AT GTC AAT	Val Asn
	Val Ile Asp					430 431
	427 428 429					
45	TAT CAT AG	gtacgtattatt.....	Intron 9	.....tatcttttaaaag	G AGC AGC	Ser Ser
	Tyr His Arg					469 470
	466 467 468					
50	TCT GTG G	gtatgtcaagct.....	Intron 10	.....aaaaatttctag	TG AAG CCA	Lys Pro
	Ser Val Val					536 537
	533 534 535					
55	CAA TGG AAG	gtaccttttact.....	Intron 11	.....cttatttttacag	ATG TAT GAG	Met Tyr Glu
	Gln Trp Lys					585 586 587
	582 583 584					
60	ATA AAA G	gtctgcagagat.....	Intron 12	.....gtcattttgcag	TT CCT ATG	Pro Met
	Ile Lys Val					639 640
	636 637 638					

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5	CTT Leu 663	TGG Trp 664	AAG Lys 665	gtattcccaatt.....	Intron 13	.....tatttactacag	CCC Pro 666	CTG Leu 667	ATG Met 668
10	AGC Ser 736	AAA Lys 737	G Val 738	gtaagaagaggt.....	Intron 14	.....ttttccctcag	TA Asn 739	AAT Ile 740	ATC
15	ATC Ile 797	CAT His 798	G Asp 799	gtaagtttacta.....	Intron 15	.....ttttctctcag	AT His 800	CAT Phe 801	TTT
20	ACT Thr 829	CAA Gln 830	G Asp 831	gtaaaaattata.....	Intron 16	.....tttctttttcag	AT Asp 832	GAT Ile 833	ATT
25	CAC His 864	CAA Gln 865	AG Arg 866	gtattgtacttg.....	Intron 17	.....tatcctttgtag	A Met 867	ATG Lys 868	AAA
30	TTT Phe 889	CAG Gln 890	AAG Lys 891	gttgctttttca.....	Intron 18	.....ttatctaaacag	AGA Arg 892	Exon A ACG Thr 893	GAC Asp 894
35	AAA	Exon A TAT	GAT	gtacatttgtct.....	Intron 18	.....cttttcttttag	Exon D CCA Pro 892	GAA Glu 893	ACG Thr 894
40							Exon B AAA Lys 892	CGT Arg 893	TTG Leu 894
45	GAA	Exon D ACC	AGA	gtatccagtggt.....	Intron 18	.....ctttttaaacag	Exon C ATG Met 892	CTT Leu 893	GAA Glu 894

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Human OB Receptor Protein, Recombinant Secreted Receptor amino acid sequence (Seq. ID. No. 10):

1 MICQKFCVVL LHWEFIYVIT AFNLSYPITP WRFKLSCMPP NSTYDYFLLP  
5 51 AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101 LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10 151 LFRNINYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201 PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
251 GNLKISWSSP PLVPFFLQYQ VKYSENSTTV IREADKIVSA TSLLVDSILP  
15 301 GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF  
351 HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSK VTFFNLNETK  
20 401 PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS  
451 TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
501 QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
25 551 IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601 PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30 651 GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701 FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
751 SSCVIVSWIL SPSDYKL MYF IIEWKNLNED GEIKWLR ISS SVKKYYIHDH  
35 801 FIPIEKYQFS LYPIFMEGVG KP KIINSFTQ DDIEKHQSD

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Human OB Receptor Protein, Recombinant Secreted Receptor DNA  
sequence (Seq. ID. No. 11):

```
5   1   GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC
    51   GGTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT
    101  TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA
10   151  TAACTGCGTT TAACTTGTCA TATCCAATTA CTCCTTGAG AGTTAAGTTG
    201  TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG
    251  GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG
    301  AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA
    351  ACTTTCCACT GTTGCTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG
20   401  TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG
    451  TTTTTCACAA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA
    501  GACTTAAAAT TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT
25   551  CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT
    601  TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTC A GATGGTTCAC
30   651  TGCAATTGCA GTGTTACGAA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC
    701  AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG
    751  GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG
    801  AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA
    851  TTTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATTT CCACTTCAAT
40   901  ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC
    951  AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC
    1001  TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT
    1051  GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC
    1101  TTTCCACCTA AAATTCTGAC AAGTGTTGGG TCTAATGTTT CTTTTCCTG
50   1151  CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT
    1201  GGATGAATTT AGCTGAGAAA ATTCCTCAAA GCCAGTATGA TGTTGTGAGT
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1251 GATCATGTTA GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG  
1301 AGGAAAAGTTT ACCTATGATG CAGTGTACTG CTGCAATGAA CATGAATGCC  
5 1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA  
1401 TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG  
10 1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA  
1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC  
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC  
15 1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC  
1651 TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG  
20 1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG  
1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC  
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGA AAGAAGTACA ATGGAAGATG  
25 1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA  
1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC  
30 1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT  
2001 ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA  
2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA  
35 2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT  
2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC  
40 2201 TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT  
2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG  
2301 AGCAAAGTAA ATATCGTGCA GTCACCTAGT GCTTATCCTT TAAACAGCAG  
45 2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT  
2401 ATTTTATTAT TGAGTGGA AATCTTAATG AAGATGGTGA AATAAAATGG  
50 2451 CTTAGAATCT CTTCATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT  
2501 CCCCATGAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG

- 85 -

2551 TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA

2601 CACCAGAGTG ATTGATAAGG ATCC

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Human OB Receptor Protein, Recombinant Secreted Receptor DNA  
sequence with C-terminal FLAG (Seq. ID. No. 12):

5  
1. CCATTGAAGT CAATGGGAGT TTGTTTGGC ACCAAAATCA ACGGGGATTT  
51 CCAAAATGTC GTAATAACCC CGCCCCGTTG ACGCAAATGG GCGGTAGGCG  
10 101 TGTACGGTGG GAGGTCTATA TAAGCAGAGC TCGTTTAGTG AACCGTCAGA  
151 TCTCTAGAAG CTGGGTACCA GCTGCTAGCA AGCTTGCTAG CGGCCGCCAG  
201 TGTGATGGAT ATCTGCAGAA TTCGGCTTTC TCTGCCTTCG GTCGAGTTGG  
15 251 ACCCCCGGAT CAAGGTGTAC TTCTCTGAAG TAAGATGATT TGTCAAAAAT  
301 TCTGTGTGGT TTTGTTACAT TGGAATTTA TTTATGTGAT AACTGCGTTT  
20 351 AACTTGTCAT ATCCAATTAC TCCTTGGAGA TTTAAGTTGT CTTGCATGCC  
401 ACCAAATTCA ACCTATGACT ACTTCCTTTT GCCTGCTGGG CTCTCAAAGA  
451 AACTTCAAA TTCGAATGGA CATTATGAGA CAGCTGTTGA ACCTAAGTTT  
25 501 AATTCAAGTG GTA CTCACTT TTCTAACTTA TCCAAAACAA CTTTCCACTG  
551 TTGCTTTCGG AGTGAGCAAG ATAGAACTG CTCCTTATGT GCAGACAACA  
30 601 TTGAAGGAAA GACATTTGTT TCAACAGTAA ATTCTTTAGT TTTTCAACAA  
651 ATAGATGCAA ACTGGAACAT ACAGTGCTGG CTAAAAGGAG ACTTAAAATT  
701 ATTCATCTGT TATGTGGAGT CATTATTTAA GAATCTATTC AGGAATTATA  
35 751 ACTATAAGGT CCATCTTTTA TATGTTCTGC CTGAAGTGTT AGAAGATTCA  
801 CCTCTGGTTC CCCAAAAGG CAGTTTTTCAG ATGGTTCACT GCAATTGCAG  
40 851 TGTTACGAA TGTTGTGAAT GTCTTGCGC TGTGCCAACA GCCAAACTCA  
901 ACGACACTCT CCTTATGTGT TTGAAAATCA CATCTGGTGG AGTAATTTTC  
951 CAGTCACCTC TAATGTCAGT TCAGCCCATA AATATGGTGA AGCCTGATCC  
45 1001 ACCATTAGGT TTGCATATGG AAATCACAGA TGATGGTAAT TTAAAGATTT  
1051 CTTGGTCCAG CCCACCATTG GTACCATTTC CACTTCAATA TCAAGTGAAA  
50 1101 TATTCAGAGA ATTCTACAAC AGTTATCAGA GAAGCTGACA AGATTGTCTC  
1151 AGCTACATCC CTGCTAGTAG ACAGTATACT TCCTGGGTCT TCGTATGAGG



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1201 TTCAGGTGAG GGGCAAGAGA CTGGATGGCC CAGGAATCTG GAGTGACTGG  
1251 AGTACTCCTC GTGTCTTTAC CACACAAGAT GTCATATACT TTCCACCTAA  
5 1301 AATTCTGACA AGTGTTGGGT CTAATGTTTC TTTTCACTGC ATCTATAAGA  
1351 AGGAAAACAA GATTGTTCCC TCAAAAGAGA TTGTTTGGTG GATGAATTTA  
1401 GCTGAGAAAA TTCCTCAAAG CCAGTATGAT GTTGTGAGTG ATCATGTTAG  
10 1451 CAAAGTTACT TTTTCAATC TGAATGAAAC CAAACCTCGA GGAAAGTTTA  
1501 CCTATGATGC AGTGTACTGC TGCAATGAAC ATGAATGCCA TCATCGCTAT  
15 1551 GCTGAATTAT ATGTGATTGA TGTCAATATC AATATCTCAT GTGAAACTGA  
1601 TGGGTACTTA ACTAAATGA CTTGCAGATG GTCAACCAGT ACAATCCAGT  
1651 CACTTGCGGA AAGCACTTTG CAATTGAGGT ATCATAGGAG CAGCCTTTAC  
20 1701 TGTCTGATA TTCCATCTAT TCATCCATA TCTGAGCCCA AAGATTGCTA  
1751 TTTGCAGAGT GATGGTTTTT ATGAATGCAT TTTCCAGCCA ATCTTCCTAT  
25 1801 TATCTGGCTA CACAATGTGG ATTAGGATCA ATCACTCTCT AGGTTCCTT  
1851 GACTCTCCAC CAACATGTGT CCTTCCTGAT TCTGTGGTGA AGCCACTGCC  
1901 TCCATCCAGT GTGAAAGCAG AAATTACTAT AAACATTGGA TTATTGAAAA  
30 1951 TATCTTGGGA AAAGCCAGTC TTTCCAGAGA ATAACCTTCA ATTCCAGATT  
2001 CGCTATGGTT TAAGTGGAAG AGAAGTACAA TGGAAGATGT ATGAGGTTTA  
35 2051 TGATGCAAAA TCAAAATCTG TCAGTCTCCC AGTTCCAGAC TTGTGTGCAG  
2101 TCTATGCTGT TCAGGTGCGC TGTAAGAGGC TAGATGGACT GGGATATTGG  
2151 AGTAATTGGA GCAATCCAGC CTACACAGTT GTCATGGATA TAAAAGTTCC  
40 2201 TATGAGAGGA CCTGAATTTT GGAGAATAAT TAATGGAGAT ACTATGAAAA  
2251 AGGAGAAAAA TGTCACCTTA CTTTGAAGC CCCTGATGAA AAATGACTCA  
45 2301 TTGTGCAGTG TTCAGAGATA TGTGATAAAC CATCATACTT CCTGCAATGG  
2351 AACATGGTCA GAAGATGTGG GAAATCACAC GAAATTCCTT TTCCTGTGGA  
2401 CAGAGCAAGC ACATACTGTT ACGGTTCTGG CCATCAATTC AATTGGTGCT  
50 2451 TCTGTTGCAA ATTTTAATTT AACCTTTTCA TGGCCTATGA GCAAAGTAAA  
2501 TATCGTGCAG TCACTCAGTG CTTATCCTTT AAACAGCAGT TGTGTGATTG

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2551 TTTCCTGGAT ACTATCACCC AGTGATTACA AGCTAATGTA TTTTATTATT  
2601 GAGTGGAAAA ATCTTAATGA AGATGGTGAA ATAAAATGGC TTAGAATCTC  
5 2651 TTCATCTGTT AAGAAGTATT ATATCCATGA TCATTTTATC CCCATTGAGA  
2701 AGTACCAGTT CAGTCTTTAC CCAATATTTA TGGAAGGAGT GGGAAAACCA  
10 2751 AAGATAATTA ATAGTTTCAC TCAAGATGAT ATTGAAAAAC ACCAGAGTGA  
2801 TGCAGGTGAC TACAAGGACG ACGATGACAA GTAGGGATCC AGACATGATA  
2851 AGATACATTG ATGAGTTTGG ACAACCCACA ACTAGAATGC AGTGAAAAAA  
15 2901 ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTT GTAACCAT

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Recombinant Human OB Receptor Protein, Natural Splice Variant  
amino acid sequence (Seq. ID. No. 13)

5    1    MICQKFCVVL LHWEFIYVIT AFNLSYPITP WREKLSCMPP NSTYDYFLLP  
51    AGLSKNTSNS NGHYETAVEP KFNSSGTHFS NLSKTTFHCC FRSEQDRNCS  
101    LCADNIEGKT FVSTVNSLVF QQIDANWNIQ CWLKGDLKLF ICYVESLFKN  
10    151    LFRNYNYKVH LLYVLPEVLE DSPLVPQKGS FQMVHCNCSV HECCECLVPV  
201    PTAKLNDTLL MCLKITSGGV IFQSPLMSVQ PINMVKPDPP LGLHMEITDD  
15    251    GNLKISWSSP PLVPFPLOQY VKYSENSTTV IREADKIVSA TSLLVDSILP  
301    GSSYEVQVRG KRLDGPGIWS DWSTPRVFTT QDVIYFPPKI LTSVGSNVSF  
351    HCIYKKENKI VPSKEIVWWM NLAEKIPQSQ YDVVSDHVSX VTFFNLNETK  
20    401    PRGKFTYDAV YCCNEHECHH RYAELYVIDV NINISCETDG YLTKMTCRWS  
451    TSTIQSLAES TLQLRYHRSS LYCSDIPSIH PISEPKDCYL QSDGFYECIF  
25    501    QPIFLLSGYT MWIRINHSLG SLDSPPTCVL PDSVVKPLPP SSVKAEITIN  
551    IGLLKISWEK PVFPENNLQF QIRYGLSGKE VQWKMYEVYD AKSKSVSLPV  
601    PDLCAVYAVQ VRCKRLDGLG YWSNWSNPAY TVVMDIKVPM RGPEFWRIIN  
30    651    GDTMKKEKNV TLLWKPLMKN DSLCSVQRYV INHHTSCNGT WSEDVGNHTK  
701    FTFLWTEQAH TVTVLAINSI GASVANFNLT FSWPMSKVNI VQSL SAYPLN  
35    751    SSCVIVSWIL SPSDYKLMYF IIEWKNLNEG GEIKWLRISX SVKKYYIHGK  
801    FTIL

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Human OB Receptor Protein, Natural Splice Variant DNA (Seq. ID. No. 14)

1 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC  
5 51 GGTTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT  
101 TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA  
10 151 TAACTGCGTT TAACTTGTC AATCCAATTA CTCCTTGGAG ATTTAAGTTG  
201 TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG  
251 GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG  
15 301 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA  
351 ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG  
20 401 TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG  
451 TTTTTCACAA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA  
501 GACTTAAAAT TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT  
25 551 CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT  
601 TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTC AATGGTTCAC  
30 651 TGCAATTGCA GTGTTACGTA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC  
701 AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG  
751 GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG  
35 801 AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA  
851 TTTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTTCAAT  
40 901 ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC  
951 AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC  
1001 TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT  
45 1051 GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC  
1101 TTTCCACCTA AAATTCTGAC AAGTGTGTTG TCTAATGTTT CTTTTCCTG  
50 1151 CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAGAG ATTGTTTGGT  
1201 GGATGAATTT AGCTGAGAAA ATTCCTCAAA GCCAGTATGA TGTTGTGAGT

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1251 GATCATGTTA GCAAAGTTAC TTTTTCAT CTGAATGAAA CCAAACCTCG  
1301 AGGAAAGTTT ACCTATGATG CAGTGTACTG CTGCAATGAA CATGAATGCC  
5 1351 ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA  
1401 TGTGAAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG  
1451 TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA  
10 1501 GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC  
1551 AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC  
15 1601 AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC  
1651 TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG  
1701 AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG  
20 1751 ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC  
1801 AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG  
25 1851 TATGAGGTTT ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA  
1901 CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC  
1951 TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT  
30 2001 ATAAAAGTTC CTATGAGAGG ACCTGAATT TGGAGAATAA TTAATGGAGA  
2051 TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA  
35 2101 AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT  
2151 TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC  
2201 TTTCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT  
40 2251 CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG  
2301 AGCAAAGTAA ATATCGTGCA GTCCTCAGT GCTTATCCTT TAAACAGCAG  
45 2351 TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT  
2401 ATTTTATTAT TGAGTGGAAA AATCTTAATG AAGATGGTGA AATAAAATGG  
2451 CTTAGAATCT CTTATCTGT TAAGAAGTAT TATATCCATG GTAAGTTTAC  
50 2501 TATACTT

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While the present invention has been described in terms of preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended  
5 claims cover all such equivalent variations which come within the scope of the invention as claimed.

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## SEQUENCE LISTING

## 5 (1) GENERAL INFORMATION:

(i) APPLICANT: CHANG, MING-SHI  
WELCHER, ANDREW A.  
FLETCHER, FREDERICK A.

10

(ii) TITLE OF INVENTION: OB PROTEIN RECEPTOR AND RELATED  
COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 33

15

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Amgen Inc.  
(B) STREET: 1840 Dehavilland Drive  
(C) CITY: Thousand Oaks  
(D) STATE: California  
(E) COUNTRY: USA  
(F) ZIP: 91320

20

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

25

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:

30

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Pessin, Karol M.  
(C) REFERENCE/DOCKET NUMBER: A-382-A

35

## 40 (2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 965 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

45

(ii) MOLECULE TYPE: protein

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

5	Met	Ile	Cys	Gln	Lys	Phe	Cys	Val	Val	Leu	Leu	His	Trp	Glu	Phe	Ile	1	5	10	15
	Tyr	Val	Ile	Thr	Ala	Phe	Asn	Leu	Ser	Tyr	Pro	Ile	Thr	Pro	Trp	Arg	20	25	30	
10	Phe	Lys	Leu	Ser	Cys	Met	Pro	Pro	Asn	Ser	Thr	Tyr	Asp	Tyr	Phe	Leu	35	40	45	
	Leu	Pro	Ala	Gly	Leu	Ser	Lys	Asn	Thr	Ser	Asn	Ser	Asn	Gly	His	Tyr	50	55	60	
15	Glu	Thr	Ala	Val	Glu	Pro	Lys	Phe	Asn	Ser	Ser	Gly	Thr	His	Phe	Ser	65	70	75	80
	Asn	Leu	Ser	Lys	Thr	Thr	Phe	His	Cys	Cys	Phe	Arg	Ser	Glu	Gln	Asp	85	90	95	
20	Arg	Asn	Cys	Ser	Leu	Cys	Ala	Asp	Asn	Ile	Glu	Gly	Lys	Thr	Phe	Val	100	105	110	
	Ser	Thr	Val	Asn	Ser	Leu	Val	Phe	Gln	Gln	Ile	Asp	Ala	Asn	Trp	Asn	115	120	125	
25	Ile	Gln	Cys	Trp	Leu	Lys	Gly	Asp	Leu	Lys	Leu	Phe	Ile	Cys	Tyr	Val	130	135	140	
30	Glu	Ser	Leu	Phe	Lys	Asn	Leu	Phe	Arg	Asn	Tyr	Asn	Tyr	Lys	Val	His	145	150	155	160
	Leu	Leu	Tyr	Val	Leu	Pro	Glu	Val	Leu	Glu	Asp	Ser	Pro	Leu	Val	Pro	165	170	175	
35	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	180	185	190	
40	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	195	200	205	
	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	210	215	220	
45	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	225	230	235	240
	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	245	250	255	
50	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	260	265	270	



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	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285
5	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300
10	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	315
	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335
15	Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys	340	345	350
	Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp	355	360	365
20	Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val	370	375	380
25	Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys	385	390	395
	Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His	405	410	415
30	Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile	420	425	430
	Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg	435	440	445
35	Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu	450	455	460
40	Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His	465	470	475
	Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr	485	490	495
45	Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp	500	505	510
	Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys	515	520	525
50	Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys	530	535	540

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	Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys	545	550	555	560
5	Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu	565	570	575	
	Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys	580	585	590	
10	Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala	595	600	605	
	Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn	610	615	620	
15	Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met	625	630	635	640
	Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys	645	650	655	
20	Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser	660	665	670	
	Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn	675	680	685	
	Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu	690	695	700	
30	Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile	705	710	715	720
	Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser	725	730	735	
35	Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser	740	745	750	
	Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met	755	760	765	
	Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys	770	775	780	
45	Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His	785	790	795	800
	Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met	805	810	815	
50	Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp	820	825	830	

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Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val  
                     835                                    840                                    845  
 5     Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His  
                     850                                    855                                    860  
 Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn  
                     865                                    870                                    875                                    880  
 10     Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Arg Thr Asp Ile Leu  
                                     885                                    890                                    895  
 Ser Leu Ile Met Ile Thr Thr Asp Glu Pro Asn Val Pro Thr Ser Gln  
                                     900                                    905                                    910  
 15     Gln Ser Ile Glu Tyr Lys Ile Phe Thr Phe Arg Arg Gly Ala Asn Leu  
                                     915                                    920                                    925  
 20     Lys Lys Ile Gln Leu Asn Phe Glu Leu Thr Tyr Gly Gly Leu Cys Phe  
                                     930                                    935                                    940  
 Arg Thr Asn Arg Cys Val Asn Leu Gly Ser Lys Cys Arg Phe Glu Ser  
                     945                                    950                                    955                                    960  
 25     Ser Leu Asp Val Leu  
                                     965

## (2) INFORMATION FOR SEQ ID NO:2:

30     (i) SEQUENCE CHARACTERISTICS:  
        (A) LENGTH: 3193 base pairs  
        (B) TYPE: nucleic acid  
        (C) STRANDEDNESS: single  
 35     (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

45     CCGCCGCCAT CTCTGCCTTC GGTTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA     60  
        GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA     120  
        TAACTGCGTT TAACTTGTCA TATCCAATTA CTCCTTGGAG ATTTAAGTTG TCTTGCATGC     180  
 50     CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA     240  
        ATTCGAATGG ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT     300

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	TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAAACT	360
	GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTTGT TTCAACAGTA AATTCTTTAG	420
5	TTTTTCAACA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA GACTTAAAT	480
	TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG	540
	TCCATCTTTT ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG	600
10	GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA TGTCTTGTGC	660
	CTGTGCCAAC AGCCAAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG	720
15	GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG AAGCCTGATC	780
	CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA TTAAAGATT TCTTGGTCCA	840
	GCCCACCATT GGTACCATT CCACCTTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA	900
20	CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC	960
	TTCCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT	1020
25	GGAGTGA CTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC TTTCCACCTA	1080
	AAATTCTGAC AAGTGTGGG TCTAATGTTT CTTTTCACTG CATCTATAAG AAGGAAAACA	1140
	AGATTGTTCC CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAA	1200
30	GCCAGTATGA TGTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTCAAT CTGAATGAA	1260
	CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGTACTG CTGCAATGAA CATGAATGCC	1320
35	ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA TGTGAACTG	1380
	ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCACCAG TACAATCCAG TCACTTGCGG	1440
	AAAGCACTTT GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA	1500
40	TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA	1560
	TTTTCCAGCC AATCTTCCTA TTATCTGGCT ACACAATGTG GATTAGGATC AATCACTCTC	1620
45	TAGGTTCACT TGA CTCTCCA CCAACATGTG TCCTTCCTGA TTCTGTGGTG AAGCCACTGC	1680
	CTCCATCCAG TGTGAAAGCA GAAATTACTA TAAACATTGG ATTATTGAAA ATATCTTGGG	1740
	AAAAGCCAGT CTTTCCAGAG AATAACCTTC AATTCCAGAT TCGCTATGGT TTAAGTGGA	1800
50	AAGAAGTACA ATGGAAGATG TATGAGGTTT ATGATGCAA ATCAAATCT GTCAGTCTCC	1860
	CAGTTCCAGA CTTGTGTGCA GTCTATGCTG TTCAGGTGCG CTGTAAGAGG CTAGATGGAC	1920

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	TGGGATATTG GAGTAATTGG AGCAATCCAG CCTACACAGT TGTCATGGAT ATAAAAGTTC	1980
	CTATGAGAGG ACCTGAATTT TGGAGAATAA TTAATGGAGA TACTATGAAA AAGGAGAAAA	2040
5	ATGTCACTTT ACTTTGGAAG CCCCTGATGA AAAATGACTC ATTGTGCAGT GTTCAGAGAT	2100
	ATGTGATAAA CCATCATACT TCCTGCAATG GAACATGGTC AGAAGATGTG GGAAATCACA	2160
10	CGAAATTCAC TTTCCTGTGG ACAGAGCAAG CACATACTGT TACGGTTCTG GCCATCAATT	2220
	CAATTGGTGC TTCTGTTGCA AATTTTAATT TAACCTTTTC ATGGCCTATG AGCAAAGTAA	2280
	ATATCGTGCA GTCACTCAGT GCTTATCCTT TAAACAGCAG TTGTGTGATT GTTTCCTGGA	2340
15	TACTATCACC CAGTGATTAC AAGCTAATGT ATTTTATTAT TGAGTGGAAA AATCTTAATG	2400
	AAGATGGTGA AATAAAATGG CTTAGAATCT CTTCATCTGT TAAGAAGTAT TATATCCATG	2460
20	ATCATTTTAT CCCCATTTAG AAGTACCAGT TCAGTCTTTA CCCAATATTT ATGGAAGGAG	2520
	TGGGAAAACC AAAGATAATT AATAGTTTCA CTCAAGATGA TATTGAAAAA CACCAGAGTG	2580
	ATGCAGGTTT ATATGTAATT GTGCCAGTAA TTATTTCTCT TTCCATCTTA TTGCTTGGAA	2640
25	CATTATTAAT ATCACACCAA AGAATGAAAA AGCTATTTTG GGAAGATGTT CCGAACCCCA	2700
	AGAATTGTTC CTGGGCACAA GGACTTAATT TTCAGAAGAG AACGGACATT CTTTGAAGTC	2760
30	TAATCATGAT CACTACAGAT GAACCCAATG TGCCAACTTC CCAACAGTCT ATAGAGTATT	2820
	AGAAGATTTT TACATTTTGA AGAAGGGGAG CAAATCTAAA AAAAATTCAG TTGAACTTCT	2880
	GAGAGTTAAC ATATGGTGGA TTATGTTGAT TTAGAACTTA AAATAGATGT GTAAATTTGG	2940
35	GTTCAAAATG TAGATTTGAG TCCAGTTTGG ATGTGTGATT AATTTTCAAA TCATCTAAAG	3000
	TTTAAAAGTA GTATTCATGA TTTCTGGCTT TTGATTTGCC ATATTCCTGG TCATAAAACA	3060
40	TTAAGAAAAT TATGGCTGTT GCTGTCATTA CATATCTATT AAATGTCATC AAATATGTAG	3120
	TAGACAATTT TGTAATTAGG TGAACCTCTAA AACTGCAACA TCTGACAAAT TGCTTTAAAA	3180
45	ATACAATGAT TAT	3193

(2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- |    |                             |
|----|-----------------------------|
| 50 | (A) LENGTH: 995 amino acids |
|    | (B) TYPE: amino acid        |
|    | (C) STRANDEDNESS: single    |
|    | (D) TOPOLOGY: linear        |

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(ii) MOLECULE TYPE: protein

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile  
 1 5 10 15  
 Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg  
 20 25 30  
 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu  
 35 40 45  
 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr  
 50 55 60  
 Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser  
 65 70 75 80  
 Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp  
 85 90 95  
 Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val  
 100 105 110  
 Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn  
 115 120 125  
 Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val  
 130 135 140  
 Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His  
 145 150 155 160  
 Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro  
 165 170 175  
 Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu  
 180 185 190  
 Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr  
 195 200 205  
 Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser  
 210 215 220  
 Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro  
 225 230 235 240

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	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	
					245					250					255		
5	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	
				260					265					270			
	Tyr	Ser	Glu	Asn	Ser	Thr	Thr	Val	Ile	Arg	Glu	Ala	Asp	Lys	Ile	Val	
			275					280					285				
10	Ser	Ala	Thr	Ser	Leu	Leu	Val	Asp	Ser	Ile	Leu	Pro	Gly	Ser	Ser	Tyr	
		290					295					300					
	Glu	Val	Gln	Val	Arg	Gly	Lys	Arg	Leu	Asp	Gly	Pro	Gly	Ile	Trp	Ser	
15		305				310					315					320	
	Asp	Trp	Ser	Thr	Pro	Arg	Val	Phe	Thr	Thr	Gln	Asp	Val	Ile	Tyr	Phe	
					325					330					335		
20	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
				340					345					350			
	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
			355					360					365				
25	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
		370					375					380					
	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
30		385				390					395					400	
	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
					405					410					415		
	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
35				420					425					430			
	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
			435					440					445				
40	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
		450					455					460					
	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His	
45		465				470					475					480	
	Pro	Ile	Ser	Glu	Pro	Lys	Asp	Cys	Tyr	Leu	Gln	Ser	Asp	Gly	Phe	Tyr	
					485					490					495		
50	Glu	Cys	Ile	Phe	Gln	Pro	Ile	Phe	Leu	Leu	Ser	Gly	Tyr	Thr	Met	Trp	
				500					505					510			
	Ile	Arg	Ile	Asn	His	Ser	Leu	Gly	Ser	Leu	Asp	Ser	Pro	Pro	Thr	Cys	
			515					520					525				

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	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys	
	530							535					540				
5	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys	
	545					550					555					560	
	Pro	Val	Phe	Pro	Glu	Asn	Asn	Leu	Gln	Phe	Gln	Ile	Arg	Tyr	Gly	Leu	
					565					570					575		
10	Ser	Gly	Lys	Glu	Val	Gln	Trp	Lys	Met	Tyr	Glu	Val	Tyr	Asp	Ala	Lys	
				580					585					590			
	Ser	Lys	Ser	Val	Ser	Leu	Pro	Val	Pro	Asp	Leu	Cys	Ala	Val	Tyr	Ala	
15				595				600					605				
	Val	Gln	Val	Arg	Cys	Lys	Arg	Leu	Asp	Gly	Leu	Gly	Tyr	Trp	Ser	Asn	
	610						615					620					
20	Trp	Ser	Asn	Pro	Ala	Tyr	Thr	Val	Val	Met	Asp	Ile	Lys	Val	Pro	Met	
	625					630					635					640	
	Arg	Gly	Pro	Glu	Phe	Trp	Arg	Ile	Ile	Asn	Gly	Asp	Thr	Met	Lys	Lys	
					645					650					655		
25	Glu	Lys	Asn	Val	Thr	Leu	Leu	Trp	Lys	Pro	Leu	Met	Lys	Asn	Asp	Ser	
				660					665					670			
	Leu	Cys	Ser	Val	Gln	Arg	Tyr	Val	Ile	Asn	His	His	Thr	Ser	Cys	Asn	
30				675				680					685				
	Gly	Thr	Trp	Ser	Glu	Asp	Val	Gly	Asn	His	Thr	Lys	Phe	Thr	Phe	Leu	
	690					695						700					
35	Trp	Thr	Glu	Gln	Ala	His	Thr	Val	Thr	Val	Leu	Ala	Ile	Asn	Ser	Ile	
	705					710					715					720	
	Gly	Ala	Ser	Val	Ala	Asn	Phe	Asn	Leu	Thr	Phe	Ser	Trp	Pro	Met	Ser	
					725					730					735		
40	Lys	Val	Asn	Ile	Val	Gln	Ser	Leu	Ser	Ala	Tyr	Pro	Leu	Asn	Ser	Ser	
				740					745					750			
	Cys	Val	Ile	Val	Ser	Trp	Ile	Leu	Ser	Pro	Ser	Asp	Tyr	Lys	Leu	Met	
45				755				760					765				
	Tyr	Phe	Ile	Ile	Glu	Trp	Lys	Asn	Leu	Asn	Glu	Asp	Gly	Glu	Ile	Lys	
	770						775					780					
50	Trp	Leu	Arg	Ile	Ser	Ser	Ser	Val	Lys	Lys	Tyr	Tyr	Ile	His	Asp	His	
	785						790				795					800	



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Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pr Ile Phe Met  
                             805                            810                            815  
 5      Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp  
                             820                            825                            830  
       Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val  
                             835                            840                            845  
 10     Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His  
                             850                            855                            860  
       Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn  
       865                            870                            875                            880  
 15     Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Lys Arg Leu Ser Ile  
                             885                            890                            895  
       Phe Leu Ser Ser Ile Gln His Gln His Val Val Leu Phe Phe Trp Ser  
                             900                            905                            910  
       Leu Lys Gln Phe Gln Lys Ile Ser Val Leu Ile His His Gly Lys Ile  
                             915                            920                            925  
 25     Lys Met Arg Cys Gln Gln Leu Trp Ser Leu Tyr Phe Gln Gln Gln Ile  
                             930                            935                            940  
       Leu Lys Arg Val Leu Phe Val Leu Val Thr Ser Ser Thr Val Leu Thr  
       945                            950                            955                            960  
 30     Ser Leu Arg Leu Arg Val Leu Arg Pro Met Arg Thr Lys Ala Arg Asp  
                             965                            970                            975  
       Asn Pro Leu Leu Asn Thr Pro Arg Ser Ala Thr Leu Asn Gln Val Lys  
                             980                            985                            990  
       Leu Val Lys  
                             995

40    (2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3063 base pairs  
 (B) TYPE: nucleic acid  
 45    (C) STRANDEDNESS: single  
       (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

	CCGCCGCCAT CTCTGCCTTC GGTCGAGTTG GACCCCCGGA TCAAGGTGTA CTTCTCTGAA	60
5	GTAAGATGAT TTGTCAAAAA TTCTGTGTGG TTTTGTTACA TTGGGAATTT ATTTATGTGA	120
	TAAC TGCGTT TAAC TTGTCA TATCCAATTA CTCCTTGGAG ATTTAAGTTG TCTTGCATGC	180
	CACCAAATTC AACCTATGAC TACTTCCTTT TGCCTGCTGG ACTCTCAAAG AATACTTCAA	240
10	ATTCGAATGG ACATTATGAG ACAGCTGTTG AACCTAAGTT TAATTCAAGT GGTACTCACT	300
	TTTCTAACTT ATCCAAAACA ACTTTCCACT GTTGCTTTTCG GAGTGAGCAA GATAGAACT	360
15	GCTCCTTATG TGCAGACAAC ATTGAAGGAA AGACATTGT TTCAACAGTA AATTCTTTAG	420
	TTTTTCAACA AATAGATGCA AACTGGAACA TACAGTGCTG GCTAAAAGGA GACTTAAAT	480
	TATTCATCTG TTATGTGGAG TCATTATTTA AGAATCTATT CAGGAATTAT AACTATAAGG	540
20	TCCATCTTTT ATATGTTCTG CCTGAAGTGT TAGAAGATTC ACCTCTGGTT CCCCAAAAG	600
	GCAGTTTTCA GATGGTTCAC TGCAATTGCA GTGTTTCATGA ATGTTGTGAA TGTCTTGTGC	660
25	CTGTGCCAAC AGCCAACTC AACGACACTC TCCTTATGTG TTTGAAAATC ACATCTGGTG	720
	GAGTAATTTT CCAGTCACCT CTAATGTCAG TTCAGCCCAT AAATATGGTG AAGCCTGATC	780
	CACCATTAGG TTTGCATATG GAAATCACAG ATGATGGTAA TTTAAAGATT TCTTGGTCCA	840
30	GCCCACCATT GGTACCATT CCACCTCAAT ATCAAGTGAA ATATTCAGAG AATTCTACAA	900
	CAGTTATCAG AGAAGCTGAC AAGATTGTCT CAGCTACATC CCTGCTAGTA GACAGTATAC	960
35	TTCTGGGTC TTCGTATGAG GTTCAGGTGA GGGGCAAGAG ACTGGATGGC CCAGGAATCT	1020
	GGAGTGACTG GAGTACTCCT CGTGTCTTTA CCACACAAGA TGTCATATAC TTTCCACCTA	1080
	AAATTCTGAC AAGTGTGGG TCTAATGTTT CTTTTCCTG CATCTATAAG AAGGAAAACA	1140
40	AGATTGTTCC CTCAAAGAG ATTGTTTGGT GGATGAATTT AGCTGAGAAA ATTCCTCAA	1200
	GCCAGTATGA TGTGTGAGT GATCATGTTA GCAAAGTTAC TTTTTCAT CTGAATGAAA	1260
45	CCAAACCTCG AGGAAAGTTT ACCTATGATG CAGTGACTG CTGCAATGAA CATGAATGCC	1320
	ATCATCGCTA TGCTGAATTA TATGTGATTG ATGTCAATAT CAATATCTCA TGTGAACTG	1380
	ATGGGTACTT AACTAAAATG ACTTGCAGAT GGTCAACCAG TACAATCCAG TCACTTGC GG	1440
50	AAAGCACTTT GCAATTGAGG TATCATAGGA GCAGCCTTTA CTGTTCTGAT ATTCCATCTA	1500
	TTCATCCCAT ATCTGAGCCC AAAGATTGCT ATTTGCAGAG TGATGGTTTT TATGAATGCA	1560

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	TTTTCCAGCC	AATCTTCCTA	TTATCTGGCT	ACACAATGTG	GATTAGGATC	AATCACTCTC	1620
	TAGGTTCACT	TGACTCTCCA	CCAACATGTG	TCCTTCCTGA	TTCTGTGGTG	AAGCCACTGC	1680
5	CTCCATCCAG	TGTGAAAGCA	GAAATTACTA	TAAACATTGG	ATTATTGAAA	ATATCTTGGG	1740
	AAAAGCCAGT	CTTTCCAGAG	AATAACCTTC	AATTCCAGAT	TCGCTATGGT	TTAAGTGGA	1800
10	AAGAAGTACA	ATGGAAGATG	TATGAGGTTT	ATGATGCAAA	ATCAAAATCT	GTCAGTCTCC	1860
	CAGTTCAGA	CTTGTGTGCA	GTCTATGCTG	TTCAGGTGCG	CTGTAAGAGG	CTAGATGGAC	1920
	TGGGATATTG	GAGTAATTGG	AGCAATCCAG	CCTACACAGT	TGTCATGGAT	ATAAAAGTTC	1980
15	CTATGAGAGG	ACCTGAATTT	TGGAGAATAA	TTAATGGAGA	TACTATGAAA	AAGGAGAAAA	2040
	ATGTCACTTT	ACTTTGGAAG	CCCCTGATGA	AAAATGACTC	ATTGTGCAGT	GTTTCAGAGAT	2100
20	ATGTGATAAA	CCATCATACT	TCCTGCAATG	GAACATGGTC	AGAAGATGTG	GGAAATCACA	2160
	CGAAATTCAC	TTTCCTGTGG	ACAGAGCAAG	CACATACTGT	TACGGTTCTG	GCCATCAATT	2220
	CAATTGGTGC	TTCTGTTGCA	AATTTTAATT	TAACCTTTTC	ATGGCCTATG	AGCAAAGTAA	2280
25	ATATCGTGCA	GTCACCTCAGT	GCTTATCCTT	TAAACAGCAG	TTGTGTGATT	GTTTCCTGGA	2340
	TACTATCACC	CAGTGATTAC	AAGCTAATGT	ATTTTATTAT	TGAGTGGAAA	AATCTTAATG	2400
30	AAGATGGTGA	AATAAAATGG	CTTAGAATCT	CTTCATCTGT	TAAGAAGTAT	TATATCCATG	2460
	ATCATTTTAT	CCCCATTGAG	AAGTACCAGT	TCAGTCTTTA	CCCAATATTT	ATGGAAGGAG	2520
	TGGGAAAACC	AAAGATAATT	AATAGTTTCA	CTCAAGATGA	TATTGAAAAA	CACCAGAGTG	2580
35	ATGCAGGTTT	ATATGTAATT	GTGCCAGTAA	TTATTTCTCTC	TTCCATCTTA	TTGCTTGGA	2640
	CATTATTAAT	ATCACACCAA	AGAATGAAAA	AGCTATTTTG	GGAAGATGTT	CCGAACCCCA	2700
40	AGAATTGTTC	CTGGGCACAA	GGACTTAATT	TTCAGAAGAA	ACGTTTGAGC	ATCTTTTTAT	2760
	CAAGCATACA	GCATCAGTGA	CATGTGGTCC	TCTTCTTTTG	GAGCCTGAAA	CAATTTTACA	2820
	AGATATCAGT	GTTGATACAT	CATGGAAAAA	TAAAGATGAG	ATGATGCCAA	CAACTGTGGT	2880
45	CTCTCTACTT	TCAACAACAG	ATCTTGAAAA	GGGTTCTGTT	TGTTTTAGTG	ACCAGTTCAA	2940
	CAGTGTTAAC	TTCTCTGAGG	CTGAGGGTAC	TGAGGTAACC	TATGAGGACG	AAAGCCAGAG	3000
50	ACAACCCTTT	GTTAAATACG	CCACGCTGAT	CAGCAACTCT	AAACCAAGTG	AAACTGGTGA	3060
	AGA						3063

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## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 969 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile  
 1 5 10 15

Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg  
 20 25 30

Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu  
 35 40 45

Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr  
 50 55 60

Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser  
 65 70 75 80

Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp  
 85 90 95

Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val  
 100 105 110

Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn  
 115 120 125

Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val  
 130 135 140

Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His

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	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	
	210						215					220					
5	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	
	225					230					235					240	
	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	
					245					250					255		
10	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	
				260					265					270			
	Tyr	Ser	Glu	Asn	Ser	Thr	Thr	Val	Ile	Arg	Glu	Ala	Asp	Lys	Ile	Val	
15			275					280					285				
	Ser	Ala	Thr	Ser	Leu	Leu	Val	Asp	Ser	Ile	Leu	Pro	Gly	Ser	Ser	Tyr	
		290					295					300					
20	Glu	Val	Gln	Val	Arg	Gly	Lys	Arg	Leu	Asp	Gly	Pro	Gly	Ile	Trp	Ser	
	305					310					315					320	
	Asp	Trp	Ser	Thr	Pro	Arg	Val	Phe	Thr	Thr	Gln	Asp	Val	Ile	Tyr	Phe	
				325						330					335		
25	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
				340					345					350			
	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
30			355					360					365				
	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
		370					375					380					
	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
35		385				390					395					400	
	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
				405						410					415		
40	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
				420				425					430				
	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
45			435					440					445				
	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
		450					455					460					
	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His	
50		465				470					475					480	

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	Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr	485	490	495
5	Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp	500	505	510
	Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys	515	520	525
10	Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys	530	535	540
	Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys	545	550	555
15	Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu	565	570	575
	Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys	580	585	590
20	Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala	595	600	605
	Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn	610	615	620
	Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met	625	630	635
30	Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys	645	650	655
	Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser	660	665	670
35	Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn	675	680	685
	Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu	690	695	700
	Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile	705	710	715
45	Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser	725	730	735
	Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser	740	745	750
50	Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met	755	760	765

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Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys  
 770 775 780  
 5 Trp L u Arg Ile Ser S r Ser Val Lys Lys Tyr Tyr Ile His Asp His  
 785 790 795 800  
 Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met  
 805 810 815  
 10 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp  
 820 825 830  
 Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val  
 835 840 845  
 15 Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His  
 850 855 860  
 20 Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn  
 865 870 875 880  
 Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Met Leu Glu Gly Ser  
 885 890 895  
 25 Met Phe Val Lys Ser His His His Ser Leu Ile Ser Ser Thr Gln Gly  
 900 905 910  
 His Lys His Cys Gly Arg Pro Gln Gly Pro Leu His Arg Lys Thr Arg  
 915 920 925  
 Asp Leu Cys Ser Leu Val Tyr Leu Leu Thr Leu Pro Pro Leu Leu Ser  
 930 935 940  
 35 Tyr Asp Pro Ala Lys Ser Pro Ser Val Arg Asn Thr Gln Glu Ser Ile  
 945 950 955 960  
 Lys Lys Lys Lys Lys Lys Leu Glu Gly  
 965  
 40

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- 45 (A) LENGTH: 969 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

	Met	Ile	Cys	Gln	Lys	Phe	Cys	Val	Val	Leu	Leu	His	Trp	Glu	Phe	Ile	
	1				5					10					15		
5	Tyr	Val	Ile	Thr	Ala	Phe	Asn	Leu	Ser	Tyr	Pro	Ile	Thr	Pro	Trp	Arg	
				20					25					30			
	Phe	Lys	Leu	Ser	Cys	Met	Pro	Pro	Asn	Ser	Thr	Tyr	Asp	Tyr	Phe	Leu	
10			35					40					45				
	Leu	Pro	Ala	Gly	Leu	Ser	Lys	Asn	Thr	Ser	Asn	Ser	Asn	Gly	His	Tyr	
		50					55					60					
15	Glu	Thr	Ala	Val	Glu	Pro	Lys	Phe	Asn	Ser	Ser	Gly	Thr	His	Phe	Ser	
	65					70					75					80	
	Asn	Leu	Ser	Lys	Thr	Thr	Phe	His	Cys	Cys	Phe	Arg	Ser	Glu	Gln	Asp	
				85						90					95		
20	Arg	Asn	Cys	Ser	Leu	Cys	Ala	Asp	Asn	Ile	Glu	Gly	Lys	Thr	Phe	Val	
			100						105					110			
	Ser	Thr	Val	Asn	Ser	Leu	Val	Phe	Gln	Gln	Ile	Asp	Ala	Asn	Trp	Asn	
25			115					120					125				
	Ile	Gln	Cys	Trp	Leu	Lys	Gly	Asp	Leu	Lys	Leu	Phe	Ile	Cys	Tyr	Val	
		130					135					140					
30	Glu	Ser	Leu	Phe	Lys	Asn	Leu	Phe	Arg	Asn	Tyr	Asn	Tyr	Lys	Val	His	
	145					150					155					160	
	Leu	Leu	Tyr	Val	Leu	Pro	Glu	Val	Leu	Glu	Asp	Ser	Pro	Leu	Val	Pro	
				165						170					175		
35	Gln	Lys	Gly	Ser	Phe	Gln	Met	Val	His	Cys	Asn	Cys	Ser	Val	His	Glu	
				180					185						190		
	Cys	Cys	Glu	Cys	Leu	Val	Pro	Val	Pro	Thr	Ala	Lys	Leu	Asn	Asp	Thr	
40			195					200					205				
	Leu	Leu	Met	Cys	Leu	Lys	Ile	Thr	Ser	Gly	Gly	Val	Ile	Phe	Gln	Ser	
		210					215					220					
45	Pro	Leu	Met	Ser	Val	Gln	Pro	Ile	Asn	Met	Val	Lys	Pro	Asp	Pro	Pro	
	225					230					235					240	
	Leu	Gly	Leu	His	Met	Glu	Ile	Thr	Asp	Asp	Gly	Asn	Leu	Lys	Ile	Ser	
				245						250					255		
50	Trp	Ser	Ser	Pro	Pro	Leu	Val	Pro	Phe	Pro	Leu	Gln	Tyr	Gln	Val	Lys	
				260					265					270			



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	Tyr	Ser	Glu	Asn	Ser	Thr	Thr	Val	Ile	Arg	Glu	Ala	Asp	Lys	Ile	Val	
			275					280					285				
5	Ser	Ala	Thr	Ser	Leu	Leu	Val	Asp	Ser	Ile	Leu	Pro	Gly	Ser	Ser	Tyr	
		290					295					300					
	Glu	Val	Gln	Val	Arg	Gly	Lys	Arg	Leu	Asp	Gly	Pro	Gly	Ile	Trp	Ser	
	305					310					315					320	
10	Asp	Trp	Ser	Thr	Pro	Arg	Val	Phe	Thr	Thr	Gln	Asp	Val	Ile	Tyr	Phe	
					325					330					335		
	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
15				340					345					350			
	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
			355					360					365				
20	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
	370						375					380					
	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
	385					390					395					400	
25	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
					405					410					415		
	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
30				420					425					430			
	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
			435					440					445				
35	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
	450						455					460					
	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His	
	465					470					475					480	
40	Pro	Ile	Ser	Glu	Pro	Lys	Asp	Cys	Tyr	Leu	Gln	Ser	Asp	Gly	Phe	Tyr	
					485					490					495		
	Glu	Cys	Ile	Phe	Gln	Pro	Ile	Phe	Leu	Leu	Ser	Gly	Tyr	Thr	Met	Trp	
45				500					505					510			
	Ile	Arg	Ile	Asn	His	Ser	Leu	Gly	Ser	Leu	Asp	Ser	Pro	Pro	Thr	Cys	
			515					520					525				
50	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys	
	530						535					540					
	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys	
	545					550					555					560	

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Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu  
565 570 575

5 Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys  
580 585 590

Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala  
595 600 605

10 Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn  
610 615 620

Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met  
625 630 635 640

Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys  
645 650 655

20 Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser  
660 665 670

Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn  
675 680 685

25 Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu  
690 695 700

Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile  
705 710 715 720

Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser  
725 730 735

35 Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser  
740 745 750

Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met  
755 760 765

40 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys  
770 775 780

Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His  
785 790 795 800

Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met  
805 810 815

50 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp  
820 825 830

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Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val  
835 840 845

Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His  
5 850 855 860

Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn  
865 870 875 880

Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Met Leu Glu Gly Ser  
10 885 890 895

Met Phe Val Lys Ser His His His Ser Leu Ile Ser Ser Thr Gln Gly  
15 900 905 910

His Lys His Cys Gly Arg Pro Gln Gly Pro Leu His Arg Lys Thr Arg  
915 920 925

Asp Leu Cys Ser Leu Val Tyr Leu Leu Thr Leu Pro Pro Leu Leu Ser  
20 930 935 940

Tyr Asp Pro Ala Lys Ser Pro Ser Val Arg Asn Thr Gln Glu Ser Ile  
945 950 955 960

Lys Lys Lys Lys Lys Lys Leu Glu Gly  
25 965

## (2) INFORMATION FOR SEQ ID NO:7:

30 (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 1216 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile  
1 5 10 15

Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg  
20 25 30

Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu  
50 35 40 45

Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr  
50 55 60

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	Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser	65	70	75	80
5	Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp	85	90	95	
	Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val	100	105	110	
10	Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn	115	120	125	
	Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val	130	135	140	
15	Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His	145	150	155	160
	Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro	165	170	175	
	Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu	180	185	190	
25	Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr	195	200	205	
	Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser	210	215	220	
30	Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro	225	230	235	240
	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	245	250	255	
	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	260	265	270	
40	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285	
	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300	
45	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	315	320
	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335	

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	Pro	Pro	Lys	Ile	Leu	Thr	Ser	Val	Gly	Ser	Asn	Val	Ser	Phe	His	Cys	
				340					345					350			
5	Ile	Tyr	Lys	Lys	Glu	Asn	Lys	Ile	Val	Pro	Ser	Lys	Glu	Ile	Val	Trp	
			355					360					365				
	Trp	Met	Asn	Leu	Ala	Glu	Lys	Ile	Pro	Gln	Ser	Gln	Tyr	Asp	Val	Val	
		370					375					380					
10	Ser	Asp	His	Val	Ser	Lys	Val	Thr	Phe	Phe	Asn	Leu	Asn	Glu	Thr	Lys	
	385					390					395					400	
	Pro	Arg	Gly	Lys	Phe	Thr	Tyr	Asp	Ala	Val	Tyr	Cys	Cys	Asn	Glu	His	
15					405					410					415		
	Glu	Cys	His	His	Arg	Tyr	Ala	Glu	Leu	Tyr	Val	Ile	Asp	Val	Asn	Ile	
				420					425					430			
20	Asn	Ile	Ser	Cys	Glu	Thr	Asp	Gly	Tyr	Leu	Thr	Lys	Met	Thr	Cys	Arg	
			435					440					445				
	Trp	Ser	Thr	Ser	Thr	Ile	Gln	Ser	Leu	Ala	Glu	Ser	Thr	Leu	Gln	Leu	
		450					455						460				
25	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His	
	465					470					475					480	
	Pro	Ile	Ser	Glu	Pro	Lys	Asp	Cys	Tyr	Leu	Gln	Ser	Asp	Gly	Phe	Tyr	
30					485					490					495		
	Glu	Cys	Ile	Phe	Gln	Pro	Ile	Phe	Leu	Leu	Ser	Gly	Tyr	Thr	Met	Trp	
				500					505					510			
35	Ile	Arg	Ile	Asn	His	Ser	Leu	Gly	Ser	Leu	Asp	Ser	Pro	Pro	Thr	Cys	
			515					520					525				
	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys	
		530					535					540					
40	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys	
	545					550					555					560	
	Pro	Val	Phe	Pro	Glu	Asn	Asn	Leu	Gln	Phe	Gln	Ile	Arg	Tyr	Gly	Leu	
45					565					570					575		
	Ser	Gly	Lys	Glu	Val	Gln	Trp	Lys	Met	Tyr	Glu	Val	Tyr	Asp	Ala	Lys	
				580					585					590			
50	Ser	Lys	Ser	Val	Ser	Leu	Pro	Val	Pro	Asp	Leu	Cys	Ala	Val	Tyr	Ala	
			595					600					605				
	Val	Gln	Val	Arg	Cys	Lys	Arg	Leu	Asp	Gly	Leu	Gly	Tyr	Trp	Ser	Asn	
		610					615					620					

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	Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met	
	625	630 635 640
5	Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys	
		645 650 655
	Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser	
		660 665 670
10	Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn	
		675 680 685
	Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu	
15		690 695 700
	Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile	
		705 710 715 720
20	Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser	
		725 730 735
	Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser	
		740 745 750
25	Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met	
		755 760 765
	Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys	
30		770 775 780
	Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His	
		785 790 795 800
35	Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met	
		805 810 815
	Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp	
		820 825 830
40	Ile Glu Lys His Gln Ser Asp Ala Gly Leu Tyr Val Ile Val Pro Val	
		835 840 845
	Ile Ile Ser Ser Ser Ile Leu Leu Leu Gly Thr Leu Leu Ile Ser His	
45		850 855 860
	Gln Arg Met Lys Lys Leu Phe Trp Glu Asp Val Pro Asn Pro Lys Asn	
		865 870 875 880
50	Cys Ser Trp Ala Gln Gly Leu Asn Phe Gln Lys Pro Glu Thr Phe Glu	
		885 890 895

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	His	Leu	Phe	Ile	Lys	His	Thr	Ala	Ser	Val	Thr	Cys	Gly	Pro	Leu	Leu	
				900					905					910			
5	Leu	Glu	Pro	Glu	Thr	Ile	Ser	Glu	Asp	Ile	Ser	Val	Asp	Thr	Ser	Trp	
			915					920					925				
	Lys	Asn	Lys	Asp	Glu	Met	Met	Pro	Thr	Thr	Val	Val	Ser	Leu	Leu	Ser	
		930					935					940					
10	Thr	Thr	Asp	Leu	Glu	Lys	Gly	Ser	Val	Cys	Ile	Ser	Asp	Gln	Phe	Asn	
	945					950					955					960	
	Ser	Val	Asn	Phe	Ser	Glu	Ala	Glu	Gly	Thr	Glu	Val	Thr	Tyr	Glu	Asp	
				965						970					975		
15	Glu	Ser	Gln	Arg	Gln	Pro	Phe	Val	Lys	Tyr	Ala	Thr	Leu	Ile	Ser	Asn	
			980						985					990			
	Ser	Lys	Pro	Ser	Glu	Thr	Gly	Glu	Glu	Gln	Gly	Leu	Ile	Asn	Ser	Ser	
20			995					1000					1005				
	Val	Thr	Lys	Cys	Phe	Ser	Ser	Lys	Asn	Ser	Pro	Leu	Lys	Asp	Ser	Phe	
	1010						1015					1020					
25	Ser	Asn	Ser	Ser	Trp	Glu	Ile	Glu	Ala	Gln	Ala	Phe	Phe	Ile	Leu	Ser	
	1025					1030					1035					1040	
	Asp	Gln	His	Pro	Asn	Ile	Ile	Ser	Pro	His	Leu	Thr	Phe	Ser	Glu	Gly	
				1045						1050					1055		
30	Leu	Asp	Glu	Leu	Leu	Lys	Leu	Glu	Gly	Asn	Phe	Pro	Glu	Glu	Asn	Asn	
				1060					1065					1070			
	Asp	Lys	Lys	Ser	Ile	Tyr	Tyr	Leu	Gly	Val	Thr	Ser	Ile	Lys	Lys	Arg	
35		1075						1080					1085				
	Glu	Ser	Gly	Val	Leu	Leu	Thr	Asp	Lys	Ser	Arg	Val	Ser	Cys	Pro	Phe	
	1090						1095					1100					
40	Pro	Ala	Pro	Cys	Leu	Phe	Thr	Asp	Ile	Arg	Val	Leu	Gln	Asp	Ser	Cys	
	1105				1110						1115					1120	
	Ser	His	Phe	Val	Glu	Asn	Asn	Ile	Asn	Leu	Gly	Thr	Ser	Ser	Lys	Lys	
				1125						1130					1135		
45	Thr	Phe	Ala	Ser	Tyr	Met	Pro	Gln	Phe	Gln	Thr	Cys	Ser	Thr	Gln	Thr	
				1140					1145					1150			
	His	Lys	Ile	Met	Glu	Asn	Lys	Met	Cys	Asp	Leu	Thr	Val	Phe	His	Arg	
50		1155					1160					1165					
	Asn	Leu	Gln	Ile	Cys	Val	Ile	Met	Gly	Asn	Ile	Lys	Cys	Asn	Arg	Leu	
	1170						1175					1180					

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Leu Trp Val Gly Glu Arg Lys Glu Thr Arg Val Lys Phe Glu Asn Asn  
 1185 1190 1195 1200

5 Cys Ser Lys Lys Lys Lys Lys Lys Asn Ser Arg Pro Ala Arg Pro Asp  
 1205 1210 1215

## (2) INFORMATION FOR SEQ ID NO:8:

10

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3599 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

20

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

25 GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTCGAGTTG 60  
 GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG 120  
 TTTTGTTACA TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTC AATCCAATTA 180  
 30 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT 240  
 TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG 300  
 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAAGTT ATCCAAAACA ACTTTCCACT 360  
 35 GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA 420  
 AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA 480  
 40 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA 540  
 AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT 600  
 TAGAAGATTC ACCTCTGGTT CCCCAAAAAG GCAGTTTTCA GATGGTTTAC TGCAATTGCA 660  
 45 GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC 720  
 TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG 780  
 50 TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTGTCATATG GAAATCACAG 840  
 ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACTTCAAT 900



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	ATCAAGTGAA	ATATTCAGAG	AATTCTACAA	CAGTTATCAG	AGAAGCTGAC	AAGATTGTCT	960
	CAGCTACATC	CCTGCTAGTA	GACAGTATAC	TTCCTGGGTC	TTCGTATGAG	GTTCAGGTGA	1020
5	GGGGCAAGAG	ACTGGATGGC	CCAGGAATCT	GGAGTGACTG	GAGTACTCCT	CGTGTCTTTA	1080
	CCACACAAGA	TGTCATATAC	TTCCACCTA	AAATTCTGAC	AAGTGTGGG	TCTAATGTTT	1140
	CTTTTCACTG	CATCTATAAG	AAGGAAAACA	AGATTGTTCC	CTCAAAAGAG	ATTGTTTGGT	1200
10	GGATGAATTT	AGCTGAGAAA	ATTCCTCAA	GCCAGTATGA	TGTTGTGAGT	GATCATGTTA	1260
	GCAAAGTTAC	TTTTTTCAAT	CTGAATGAAA	CCAAACCTCG	AGGAAAGTTT	ACCTATGATG	1320
15	CAGTGACTG	CTGCAATGAA	CATGAATGCC	ATCATCGCTA	TGCTGAATTA	TATGTGATTG	1380
	ATGTCAATAT	CAATATCTCA	TGTGAACTG	ATGGGTACTT	AACTAAAATG	ACTTGCAGAT	1440
	GGTCAACCAG	TACAATCCAG	TCACTTGCGG	AAAGCACTTT	GCAATTGAGG	TATCATAGGA	1500
20	GCAGCCTTTA	CTGTTCTGAT	ATTCCATCTA	TTCATCCCAT	ATCTGAGCCC	AAAGATTGCT	1560
	ATTTGCAGAG	TGATGGTTTT	TATGAATGCA	TTTTCCAGCC	AATCTTCCTA	TTATCTGGCT	1620
25	ACACAATGTG	GATTAGGATC	AATCACTCTC	TAGGTTCACT	TGACTCTCCA	CCAACATGTG	1680
	TCCTTCCTGA	TTCTGTGGTG	AAGCCACTGC	CTCCATCCAG	TGTGAAAGCA	GAAATTACTA	1740
	TAAACATTGG	ATTATTGAAA	ATATCTTGGG	AAAAGCCAGT	CTTTCCAGAG	AATAACCTTC	1800
30	AATTCCAGAT	TCGCTATGGT	TTAAGTGGA	AAGAAGTACA	ATGGAAGATG	TATGAGGTTT	1860
	ATGATGCAAA	ATCAAAATCT	GTCAGTCTCC	CAGTTCCAGA	CTTGTGTGCA	GTCTATGCTG	1920
35	TTCAGGTGCG	CTGTAAGAGG	CTAGATGGAC	TGGGATATTG	GAGTAATTGG	AGCAATCCAG	1980
	CCTACACAGT	TGTCATGGAT	ATAAAAGTTC	CTATGAGAGG	ACCTGAATTT	TGGAGAATAA	2040
	TTAATGGAGA	TACTATGAAA	AAGGAGAAAA	ATGTCACTTT	ACTTTGGAAG	CCCCTGATGA	2100
40	AAAATGACTC	ATTGTGCAGT	GTTCAGAGAT	ATGTGATAAA	CCATCATACT	TCCTGCAATG	2160
	GAACATGGTC	AGAAGATGTG	GGAAATCACA	CGAAATTCAC	TTTCCTGTGG	ACAGAGCAAG	2220
45	CACATACTGT	TACGGTCTG	GCCATCAATT	CAATTGGTGC	TTCTGTTGCA	AATTTTAATT	2280
	TAACCTTTTC	ATGGCCTATG	AGCAAAGTAA	ATATCGTGCA	GTCACCTCAGT	GCTTATCCTT	2340
	TAAACAGCAG	TTGTGTGATT	GTTTCCTGGA	TACTATCACC	CAGTGATTAC	AAGCTAATGT	2400
50	ATTTTATTAT	TGAGTGGAAA	AATCTTAATG	AAGATGGTGA	AATAAAATGG	CTTAGAATCT	2460
	CTTCATCTGT	TAAGAAGTAT	TATATCCATG	ATCATTTTAT	CCCCATTGAG	AAGTACCAGT	2520

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	TCAGTCTTTA CCCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA	2580
	CTCAAGATGA TATTGAAAAA CACCAGAGTG ATGCAGGTTT ATATGTAATT GTGCCAGTAA	2640
5	TTATTTCTCTC TTCCATCTTA TTGCTTGGA CATTATTAAT ATCACACCAA AGAATGAAAA	2700
	AGCTATTTTG GGAAGATGTT CCGAACCCCA AGAATTGTTC CTGGGCACAA GGACTTAATT	2760
10	TTCAGAAGCC AGAAACGTTT GAGCATCTTT TTATCAAGCA TACAGCATCA GTGACATGTG	2820
	GTCCTCTTCT TTTGGAGCCT GAAACAATTT CAGAAGATAT CAGTGTTGAT ACATCATGGA	2880
	AAAATAAAGA TGAGATGATG CCAACAACCTG TGGTCTCTCT ACTTTCAACA ACAGATCTTG	2940
15	AAAAGGGTTC TGTTTGTATT AGTGACCAGT TCAACAGTGT TAACTTCTCT GAGGCTGAGG	3000
	GTACTGAGGT AACCTATGAG GACGAAAGCC AGAGACAACC CTTTGTTAAA TACGCCACGC	3060
20	TGATCAGCAA CTCTAAACCA AGTGAACTG GTGAAGAACA AGGGCTTATA AATAGTTCAG	3120
	TCACCAAGTG CTTCTCTAGC AAAAATTCTC CGTTGAAGGA TTCTTTCTCT AATAGCTCAT	3180
	GGGAGATAGA GGCCCAGGCA TTTTTTATAT TATCGGATCA GCATCCCAAC ATAATTTAC	3240
25	CACACCTCAC ATTCTCAGAA GGATTGGATG AACTTTTGAA ATTGGAGGGA AATTTCCCTG	3300
	AAGAAAATAA TGATAAAAAG TCTATCTATT ATTTAGGGGT CACCTCAATC AAAAAGAGAG	3360
30	AGAGTGGTGT GCTTTTGACT GACAAGTCAA GGGTATCGTG CCCATTCCCA GCCCCCTGTT	3420
	TATTCACGGA CATCAGAGTT CTCCAGGACA GTTGCTCACA CTTTGTAGAA AATAATATCA	3480
	ACTTAGGAAC TTCTAGTAAG AAGACTTTTG CATCTTACAT GCCTCAATTC CAAACTTGTT	3540
35	CTACTCAGAC TCATAAGATC ATGGAAAACA AGATGTGTGA CCTAACTGTG TAATCTAGA	3599

## (2) INFORMATION FOR SEQ ID NO:9:

- |    |                               |
|----|-------------------------------|
| 40 | (i) SEQUENCE CHARACTERISTICS: |
|    | (A) LENGTH: 17 base pairs     |
|    | (B) TYPE: nucleic acid        |
|    | (C) STRANDEDNESS: single      |
|    | (D) TOPOLOGY: linear          |
| 45 | (ii) MOLECULE TYPE: cDNA      |

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

NNNNNTACCT TTTCCAG

17

5 (2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 839 amino acids

(B) TYPE: amino acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

20 Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile  
1 5 10 15

Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg  
20 25 30

25 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu  
35 40 45

30 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr  
50 55 60

Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser  
65 70 75 80

35 Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp  
85 90 95

Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val  
100 105 110

40 Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn  
115 120 125

Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val  
130 135 140

45 Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His  
145 150 155 160

50 Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro  
165 170 175

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	Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu	180	185	190
5	Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr	195	200	205
	Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser	210	215	220
10	Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro	225	230	235
	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	245	250	255
15	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	260	265	270
	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285
20	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300
	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	315
25	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335
30	Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys	340	345	350
	Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp	355	360	365
35	Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val	370	375	380
	Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys	385	390	395
40	Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His	405	410	415
45	Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile	420	425	430
	Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg	435	440	445
50	Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu	450	455	460

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	Arg	Tyr	His	Arg	Ser	Ser	Leu	Tyr	Cys	Ser	Asp	Ile	Pro	Ser	Ile	His
	465					470					475					480
5	Pro	Ile	Ser	Glu	Pro	Lys	Asp	Cys	Tyr	Leu	Gln	Ser	Asp	Gly	Phe	Tyr
					485					490						495
	Glu	Cys	Ile	Phe	Gln	Pro	Ile	Phe	Leu	Leu	Ser	Gly	Tyr	Thr	Met	Trp
				500					505					510		
10	Ile	Arg	Ile	Asn	His	Ser	Leu	Gly	Ser	Leu	Asp	Ser	Pro	Pro	Thr	Cys
			515					520					525			
	Val	Leu	Pro	Asp	Ser	Val	Val	Lys	Pro	Leu	Pro	Pro	Ser	Ser	Val	Lys
15		530					535					540				
	Ala	Glu	Ile	Thr	Ile	Asn	Ile	Gly	Leu	Leu	Lys	Ile	Ser	Trp	Glu	Lys
	545					550					555					560
20	Pro	Val	Phe	Pro	Glu	Asn	Asn	Leu	Gln	Phe	Gln	Ile	Arg	Tyr	Gly	Leu
					565					570					575	
	Ser	Gly	Lys	Glu	Val	Gln	Trp	Lys	Met	Tyr	Glu	Val	Tyr	Asp	Ala	Lys
				580					585					590		
25	Ser	Lys	Ser	Val	Ser	Leu	Pro	Val	Pro	Asp	Leu	Cys	Ala	Val	Tyr	Ala
			595					600					605			
	Val	Gln	Val	Arg	Cys	Lys	Arg	Leu	Asp	Gly	Leu	Gly	Tyr	Trp	Ser	Asn
30		610					615					620				
	Trp	Ser	Asn	Pro	Ala	Tyr	Thr	Val	Val	Met	Asp	Ile	Lys	Val	Pro	Met
	625					630					635					640
35	Arg	Gly	Pro	Glu	Phe	Trp	Arg	Ile	Ile	Asn	Gly	Asp	Thr	Met	Lys	Lys
					645					650					655	
	Glu	Lys	Asn	Val	Thr	Leu	Leu	Trp	Lys	Pro	Leu	Met	Lys	Asn	Asp	Ser
				660					665					670		
40	Leu	Cys	Ser	Val	Gln	Arg	Tyr	Val	Ile	Asn	His	His	Thr	Ser	Cys	Asn
			675					680					685			
	Gly	Thr	Trp	Ser	Glu	Asp	Val	Gly	Asn	His	Thr	Lys	Phe	Thr	Phe	Leu
45		690					695					700				
	Trp	Thr	Glu	Gln	Ala	His	Thr	Val	Thr	Val	Leu	Ala	Ile	Asn	Ser	Ile
	705					710					715					720
50	Gly	Ala	Ser	Val	Ala	Asn	Phe	Asn	Leu	Thr	Phe	Ser	Trp	Pro	Met	Ser
					725					730					735	

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Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser  
 740 745 750  
 5 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met  
 755 760 765  
 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys  
 770 775 780  
 10 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Asp His  
 785 790 795 800  
 Phe Ile Pro Ile Glu Lys Tyr Gln Phe Ser Leu Tyr Pro Ile Phe Met  
 805 810 815  
 15 Glu Gly Val Gly Lys Pro Lys Ile Ile Asn Ser Phe Thr Gln Asp Asp  
 820 825 830  
 20 Ile Glu Lys His Gln Ser Asp  
 835

## (2) INFORMATION FOR SEQ ID NO:11:

25 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 2624 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: cDNA

## 35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTCGAGTTG 60  
 GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAA TTCTGTGTGG 120  
 40 TTTTGTTACA TTGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTC TATCCAATTA 180  
 CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT 240  
 45 TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG 300  
 AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA ACTTTCCACT 360  
 GTTGCTTTTCG GAGTGAGCAA GATAGAACT GCTCCTTATG TGCAGACAAC ATTGAAGGAA 420  
 50 AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA 480  
 TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA 540

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	AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT	600
5	TAGAAGATT CACCTCTGGTT CCCCCAAAAG GCAGTTTTCA GATGGTTCAC TGCAATTGCA	660
	GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAAACTC AACGACACTC	720
	TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG	780
10	TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG	840
	ATGATGGTAA TTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATTT CCACTTCAAT	900
15	ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC AAGATTGTCT	960
	CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA	1020
	GGGGCAAGAG ACTGGATGGC CCAGGAATCT GGAGTGA CTG GAGTACTCCT CGTGTCTTTA	1080
20	CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTGGG TCTAATGTTT	1140
	CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAAGAG ATTGTTTGGT	1200
25	GGATGAATTT AGCTGAGAAA ATTCTCATAA GCCAGTATGA TGTTGTGAGT GATCATGTTA	1260
	GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG	1320
	CAGTGTACTG CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG	1380
30	ATGTCAATAT CAATATCTCA TGTGAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT	1440
	GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA	1500
	GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC AAAGATTGCT	1560
35	ATTTGCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT	1620
	ACACAATGTG GATTAGGATC AATCACTCTC TAGGTTCACT TGACTCTCCA CCAACATGTG	1680
40	TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA	1740
	TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC	1800
45	AATTCCAGAT TCGCTATGGT TTAAGTGGA AAGAAGTACA ATGGAAGATG TATGAGGTTT	1860
	ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG	1920
	TTCAGGTGCG CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG	1980
50	CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA	2040
	TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCACTTT ACTTTGGAAG CCCCTGATGA	2100

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AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT TCCTGCAATG 2160  
GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG 2220  
5 CACATACTGT TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT 2280  
TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCACCTCAGT GCTTATCCTT 2340  
TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT 2400  
10 ATTTTATTAT TGAGTGGA AAAA AATCTTAATG AAGATGGTGA AATAAAATGG CTTAGAATCT 2460  
CTTCATCTGT TAAGAAGTAT TATATCCATG ATCATTTTAT CCCCATTGAG AAGTACCAGT 2520  
15 TCAGTCTTTA CCAATATTT ATGGAAGGAG TGGGAAAACC AAAGATAATT AATAGTTTCA 2580  
CTCAAGATGA TATTGAAAAA CACCAGAGTG ATTGATAAGG ATCC 2624

## (2) INFORMATION FOR SEQ ID NO:12:

20

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 2948 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

30

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCATTGAAGT CAATGGGAGT TTGTTTTGGC ACCAAAATCA ACGGGGATTT CAAAATGTC 60  
35 GTAATAACCC CGCCCCGTTG ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA 120  
TAAGCAGAGC TCGTTTAGTG AACCGTCAGA TCTCTAGAAG CTGGGTACCA GCTGCTAGCA 180  
40 AGCTTGCTAG CGGCCGCCAG TGTGATGGAT ATCTGCAGAA TTCGGCTTTC TCTGCCTTCG 240  
GTCGAGTTGG ACCCCCGGAT CAAGGTGTAC TTCTCTGAAG TAAGATGATT TGTCAAAAAT 300  
TCTGTGTGGT TTTGTTACAT TGGGAATTTA TTTATGTGAT AACTGCGTTT AACTTGTCAT 360  
45 ATCCAATTAC TCCTTGGAGA TTTAAGTTGT CTTGCATGCC ACCAAATTCA ACCTATGACT 420  
ACTTCCTTTT GCCTGCTGGG CTCTCAAAGA ATACTTCAA TTCGAATGGA CATTATGAGA 480  
50 CAGCTGTTGA ACCTAAGTTT AATTCAAGTG GTACTCACTT TTCTAACTTA TCCAAAACAA 540  
CTTCCACTG TTGCTTTCGG AGTGAGCAAG ATAGAACTG CTCCTTATGT GCAGACAACA 600



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	TTGAAGGAAA GACATTTGTT TCAACAGTAA ATTCTTTAGT TTTTCAACAA ATAGATGCAA	660
	ACTGGAACAT ACAGTGCTGG CTAAAAGGAG ACTTAAAATT ATTCATCTGT TATGTGGAGT	720
5	CATTATTTAA GAATCTATTC AGGAATTATA ACTATAAGGT CCATCTTTTA TATGTTCTGC	780
	CTGAAGTGTT AGAAGATTCA CCTCTGGTTC CCCAAAAAGG CAGTTTTCAG ATGGTTCACT	840
10	GCAATTGCAG TGTTACGAA TGTTGTGAAT GTCTTGCGCC TGTGCCAACA GCCAACTCA	900
	ACGACACTCT CTTATGTGT TTGAAAATCA CATCTGGTGG AGTAATTTTC CAGTCACCTC	960
	TAATGTCAGT TCAGCCCATTA AATATGGTGA AGCCTGATCC ACCATTAGGT TTGCATATGG	1020
15	AAATCACAGA TGATGGTAAT TTAAAGATTT CTTGGTCCAG CCCACCATTG GTACCATTTC	1080
	CACTTCAATA TCAAGTGAAA TATTCAGAGA ATTCTACAAC AGTTATCAGA GAAGCTGACA	1140
20	AGATTGTCTC AGCTACATCC CTGCTAGTAG ACAGTATACT TCCTGGGTCT TCGTATGAGG	1200
	TTCAGGTGAG GGGCAAGAGA CTGGATGGCC CAGGAATCTG GAGTGACTGG AGTACTCCTC	1260
	GTGTCTTTAC CACACAAGAT GTCATATACT TTCCACCTAA AATTCTGACA AGTGTTGGGT	1320
25	CTAATGTTTC TTTTCACTGC ATCTATAAGA AGGAAAACAA GATTGTTCCC TCAAAGAGA	1380
	TTGTTTGGTG GATGAATTTA GCTGAGAAAA TTCCTCAAAG CCAGTATGAT GTTGTGAGTG	1440
30	ATCATGTTAG CAAAGTTACT TTTTCAATC TGAATGAAAC CAAACCTCGA GGAAAGTTTA	1500
	CCTATGATGC AGTGTACTGC TGCAATGAAC ATGAATGCCA TCATCGCTAT GCTGAATTAT	1560
	ATGTGATTGA TGTCAATATC AATATCTCAT GTGAACTGA TGGGTACTTA ACTAAAATGA	1620
35	CTTGCAGATG GTCAACCAGT ACAATCCAGT CACTTGCGGA AAGCACTTTG CAATTGAGGT	1680
	ATCATAGGAG CAGCCTTTAC TGTTCTGATA TTCCATCTAT TCATCCCATTA TCTGAGCCCA	1740
40	AAGATTGCTA TTTGCAGAGT GATGGTTTTT ATGAATGCAT TTTCCAGCCA ATCTTCCTAT	1800
	TATCTGGCTA CACAATGTGG ATTAGGATCA ATCACTCTCT AGGTTCACCT GACTCTCCAC	1860
	CAACATGTGT CCTTCCTGAT TCTGTGGTGA AGCCACTGCC TCCATCCAGT GTGAAAGCAG	1920
45	AAATTACTAT AAACATTGGA TTATTGAAAA TATCTTGGA AAAGCCAGTC TTTCCAGAGA	1980
	ATAACCTTCA ATTCCAGATT CGCTATGGTT TAAGTGAAA AGAAGTACAA TGGAAGATGT	2040
50	ATGAGGTTTA TGATGCAAAA TCAAATCTG TCAGTCTCCC AGTTCCAGAC TTGTGTGCAG	2100
	TCTATGCTGT TCAGGTGCGC TGTAAGAGGC TAGATGGACT GGGATATTGG AGTAATTGGA	2160
	GCAATCCAGC CTACACAGTT GTCATGGATA TAAAAGTTCC TATGAGAGGA CCTGAATTTT	2220

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GGAGAATAAT TAATGGAGAT ACTATGAAAA AGGAGAAAAA TGTCACCTTA CTTTGGAAGC 2280  
 CCCTGATGAA AAATGACTCA TTGTGCAGTG TTCAGAGATA TGTGATAAAC CATCATACTT 2340  
 5 CCTGCAATGG AACATGGTCA GAAGATGTGG GAAATCACAC GAAATTCAC TCTCTGTGGA 2400  
 CAGAGCAAGC ACATACTGTT ACGGTTCTGG CCATCAATTC AATTGGTGCT TCTGTTGCAA 2460  
 10 ATTTTAATTT AACCTTTTCA TGGCCTATGA GCAAAGTAAA TATCGTGCAG TCACTCAGTG 2520  
 CTTATCCTTT AAACAGCAGT TGTGTGATTG TTTCTGGAT ACTATCACCC AGTGATTACA 2580  
 AGCTAATGTA TTTTATTATT GAGTGGAAAA ATCTTAATGA AGATGGTGAA ATAAAATGGC 2640  
 15 TTAGAATCTC TTCATCTGTT AAGAAGTATT ATATCCATGA TCATTTTATC CCCATTGAGA 2700  
 AGTACCAGTT CAGTCTTTAC CCAATATTTA TGGGAAGGAGT GGGAAAACCA AAGATAATTA 2760  
 20 ATAGTTTCAC TCAAGATGAT ATTGAAAAAC ACCAGAGTGA TGCAGGTGAC TACAAGGACG 2820  
 ACGATGACAA GTAGGGATCC AGACATGATA AGATACATTG ATGAGTTTGG ACAACCCACA 2880  
 ACTAGAATGC AGTGAAAAAA ATGCTTTATT TGTGAAATTT GTGATGCTAT TGCTTTATTT 2940  
 25 GTAACCAT 2948

## (2) INFORMATION FOR SEQ ID NO:13:

30 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 804 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: protein

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Ile Cys Gln Lys Phe Cys Val Val Leu Leu His Trp Glu Phe Ile  
 1 5 10 15  
 45 Tyr Val Ile Thr Ala Phe Asn Leu Ser Tyr Pro Ile Thr Pro Trp Arg  
 20 25 30  
 Phe Lys Leu Ser Cys Met Pro Pro Asn Ser Thr Tyr Asp Tyr Phe Leu  
 35 40 45  
 50 Leu Pro Ala Gly Leu Ser Lys Asn Thr Ser Asn Ser Asn Gly His Tyr  
 50 55 60

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	Glu Thr Ala Val Glu Pro Lys Phe Asn Ser Ser Gly Thr His Phe Ser	65	70	75	80
5	Asn Leu Ser Lys Thr Thr Phe His Cys Cys Phe Arg Ser Glu Gln Asp	85	90	95	
	Arg Asn Cys Ser Leu Cys Ala Asp Asn Ile Glu Gly Lys Thr Phe Val	100	105	110	
10	Ser Thr Val Asn Ser Leu Val Phe Gln Gln Ile Asp Ala Asn Trp Asn	115	120	125	
	Ile Gln Cys Trp Leu Lys Gly Asp Leu Lys Leu Phe Ile Cys Tyr Val	130	135	140	
15	Glu Ser Leu Phe Lys Asn Leu Phe Arg Asn Tyr Asn Tyr Lys Val His	145	150	155	160
	Leu Leu Tyr Val Leu Pro Glu Val Leu Glu Asp Ser Pro Leu Val Pro	165	170	175	
	Gln Lys Gly Ser Phe Gln Met Val His Cys Asn Cys Ser Val His Glu	180	185	190	
25	Cys Cys Glu Cys Leu Val Pro Val Pro Thr Ala Lys Leu Asn Asp Thr	195	200	205	
	Leu Leu Met Cys Leu Lys Ile Thr Ser Gly Gly Val Ile Phe Gln Ser	210	215	220	
30	Pro Leu Met Ser Val Gln Pro Ile Asn Met Val Lys Pro Asp Pro Pro	225	230	235	240
	Leu Gly Leu His Met Glu Ile Thr Asp Asp Gly Asn Leu Lys Ile Ser	245	250	255	
	Trp Ser Ser Pro Pro Leu Val Pro Phe Pro Leu Gln Tyr Gln Val Lys	260	265	270	
40	Tyr Ser Glu Asn Ser Thr Thr Val Ile Arg Glu Ala Asp Lys Ile Val	275	280	285	
	Ser Ala Thr Ser Leu Leu Val Asp Ser Ile Leu Pro Gly Ser Ser Tyr	290	295	300	
	Glu Val Gln Val Arg Gly Lys Arg Leu Asp Gly Pro Gly Ile Trp Ser	305	310	315	320
50	Asp Trp Ser Thr Pro Arg Val Phe Thr Thr Gln Asp Val Ile Tyr Phe	325	330	335	

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Pro Pro Lys Ile Leu Thr Ser Val Gly Ser Asn Val Ser Phe His Cys  
 340 345 350

5 Ile Tyr Lys Lys Glu Asn Lys Ile Val Pro Ser Lys Glu Ile Val Trp  
 355 360 365

Trp Met Asn Leu Ala Glu Lys Ile Pro Gln Ser Gln Tyr Asp Val Val  
 370 375 380

10 Ser Asp His Val Ser Lys Val Thr Phe Phe Asn Leu Asn Glu Thr Lys  
 385 390 395 400

Pro Arg Gly Lys Phe Thr Tyr Asp Ala Val Tyr Cys Cys Asn Glu His  
 405 410 415

15 Glu Cys His His Arg Tyr Ala Glu Leu Tyr Val Ile Asp Val Asn Ile  
 420 425 430

Asn Ile Ser Cys Glu Thr Asp Gly Tyr Leu Thr Lys Met Thr Cys Arg  
 435 440 445

20 Trp Ser Thr Ser Thr Ile Gln Ser Leu Ala Glu Ser Thr Leu Gln Leu  
 450 455 460

Arg Tyr His Arg Ser Ser Leu Tyr Cys Ser Asp Ile Pro Ser Ile His  
 465 470 475 480

Pro Ile Ser Glu Pro Lys Asp Cys Tyr Leu Gln Ser Asp Gly Phe Tyr  
 485 490 495

30 Glu Cys Ile Phe Gln Pro Ile Phe Leu Leu Ser Gly Tyr Thr Met Trp  
 500 505 510

Ile Arg Ile Asn His Ser Leu Gly Ser Leu Asp Ser Pro Pro Thr Cys  
 515 520 525

35 Val Leu Pro Asp Ser Val Val Lys Pro Leu Pro Pro Ser Ser Val Lys  
 530 535 540

Ala Glu Ile Thr Ile Asn Ile Gly Leu Leu Lys Ile Ser Trp Glu Lys  
 545 550 555 560

Pro Val Phe Pro Glu Asn Asn Leu Gln Phe Gln Ile Arg Tyr Gly Leu  
 565 570 575

45 Ser Gly Lys Glu Val Gln Trp Lys Met Tyr Glu Val Tyr Asp Ala Lys  
 580 585 590

Ser Lys Ser Val Ser Leu Pro Val Pro Asp Leu Cys Ala Val Tyr Ala  
 595 600 605

50 Val Gln Val Arg Cys Lys Arg Leu Asp Gly Leu Gly Tyr Trp Ser Asn  
 610 615 620

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Trp Ser Asn Pro Ala Tyr Thr Val Val Met Asp Ile Lys Val Pro Met  
 625 630 635 640  
 5 Arg Gly Pro Glu Phe Trp Arg Ile Ile Asn Gly Asp Thr Met Lys Lys  
 645 650 655  
 Glu Lys Asn Val Thr Leu Leu Trp Lys Pro Leu Met Lys Asn Asp Ser  
 660 665 670  
 10 Leu Cys Ser Val Gln Arg Tyr Val Ile Asn His His Thr Ser Cys Asn  
 675 680 685  
 Gly Thr Trp Ser Glu Asp Val Gly Asn His Thr Lys Phe Thr Phe Leu  
 690 695 700  
 15 Trp Thr Glu Gln Ala His Thr Val Thr Val Leu Ala Ile Asn Ser Ile  
 705 710 715 720  
 Gly Ala Ser Val Ala Asn Phe Asn Leu Thr Phe Ser Trp Pro Met Ser  
 725 730 735  
 Lys Val Asn Ile Val Gln Ser Leu Ser Ala Tyr Pro Leu Asn Ser Ser  
 740 745 750  
 25 Cys Val Ile Val Ser Trp Ile Leu Ser Pro Ser Asp Tyr Lys Leu Met  
 755 760 765  
 Tyr Phe Ile Ile Glu Trp Lys Asn Leu Asn Glu Asp Gly Glu Ile Lys  
 770 775 780  
 30 Trp Leu Arg Ile Ser Ser Ser Val Lys Lys Tyr Tyr Ile His Gly Lys  
 785 790 795 800  
 35 Phe Thr Ile Leu

## (2) INFORMATION FOR SEQ ID NO:14:

- 40 (i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 2507 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear  
 45  
 (ii) MOLECULE TYPE: cDNA

50

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

	GCGGCCGCCA GTGTGATGGA TATCTGCAGA ATTCGGCTTT CTCTGCCTTC GGTCGAGTTG	60
5	GACCCCCGGA TCAAGGTGTA CTTCTCTGAA GTAAGATGAT TTGTCAAAAA TTCTGTGTGG	120
	TTTTGTTACA TTGGGAATTT ATTTATGTGA TAACTGCGTT TAACTTGTCA TATCCAATTA	180
	CTCCTTGGAG ATTTAAGTTG TCTTGCATGC CACCAAATTC AACCTATGAC TACTTCCTTT	240
10	TGCCTGCTGG GCTCTCAAAG AATACTTCAA ATTCGAATGG ACATTATGAG ACAGCTGTTG	300
	AACCTAAGTT TAATTCAAGT GGTACTCACT TTTCTAACTT ATCCAAAACA ACTTCCACT	360
15	GTTGCTTTTC GAGTGAGCAA GATAGAACT GTCCTTATG TGCAGACAAC ATTGAAGGAA	420
	AGACATTTGT TTCAACAGTA AATTCTTTAG TTTTCAACA AATAGATGCA AACTGGAACA	480
	TACAGTGCTG GCTAAAAGGA GACTTAAAT TATTCATCTG TTATGTGGAG TCATTATTTA	540
20	AGAATCTATT CAGGAATTAT AACTATAAGG TCCATCTTTT ATATGTTCTG CCTGAAGTGT	600
	TAGAAGATTC ACCTCTGGTT CCCCAAAAG GCAGTTTTCA GATGGTTCAC TGCAATTGCA	660
25	GTGTTACGA ATGTTGTGAA TGTCTTGTGC CTGTGCCAAC AGCCAACTC AACGACACTC	720
	TCCTTATGTG TTTGAAAATC ACATCTGGTG GAGTAATTTT CCAGTCACCT CTAATGTCAG	780
	TTCAGCCCAT AAATATGGTG AAGCCTGATC CACCATTAGG TTTGCATATG GAAATCACAG	840
30	ATGATGGTAA TTTAAAGATT TCTTGGTCCA GCCCACCATT GGTACCATT CCACCTTCAAT	900
	ATCAAGTGAA ATATTCAGAG AATTCTACAA CAGTTATCAG AGAAGCTGAC AAGATTGTCT	960
35	CAGCTACATC CCTGCTAGTA GACAGTATAC TTCCTGGGTC TTCGTATGAG GTTCAGGTGA	1020
	GGGGCAAGAG ACTGGATGGC CCAGGAATCT GGAGTGACTG GAGTACTCCT CGTGTCTTTA	1080
	CCACACAAGA TGTCATATAC TTTCCACCTA AAATTCTGAC AAGTGTTGGG TCTAATGTTT	1140
40	CTTTTCACTG CATCTATAAG AAGGAAAACA AGATTGTTCC CTCAAAGAG ATTGTTTGGT	1200
	GGATGAATTT AGCTGAGAAA ATTCCTCAAA GCCAGTATGA TGTGTGAGT GATCATGTTA	1260
45	GCAAAGTTAC TTTTTTCAAT CTGAATGAAA CCAAACCTCG AGGAAAGTTT ACCTATGATG	1320
	CAGTGTACTG CTGCAATGAA CATGAATGCC ATCATCGCTA TGCTGAATTA TATGTGATTG	1380
	ATGTCAATAT CAATATCTCA TGTGAACTG ATGGGTACTT AACTAAAATG ACTTGCAGAT	1440
50	GGTCAACCAG TACAATCCAG TCACTTGCGG AAAGCACTTT GCAATTGAGG TATCATAGGA	1500
	GCAGCCTTTA CTGTTCTGAT ATTCCATCTA TTCATCCCAT ATCTGAGCCC AAAGATTGCT	1560

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1620  
1680  
1740  
1800  
1860  
1920  
1980  
2040  
2100  
2160  
2220  
2280  
2340  
2400  
2460  
2507

ATTGTCAGAG TGATGGTTTT TATGAATGCA TTTTCCAGCC AATCTTCCTA TTATCTGGCT  
ACACAATGTG GATTAGGATC AATCACTCTC TAGGTTCACT TGA CTCTCCA CCAACATGTG  
TCCTTCCTGA TTCTGTGGTG AAGCCACTGC CTCCATCCAG TGTGAAAGCA GAAATTACTA  
TAAACATTGG ATTATTGAAA ATATCTTGGG AAAAGCCAGT CTTTCCAGAG AATAACCTTC  
AATTCCAGAT TCGCTATGGT TTAAGTGGAA AAGAAGTACA ATGGAAGATG TATGAGGTTT  
ATGATGCAAA ATCAAAATCT GTCAGTCTCC CAGTTCCAGA CTTGTGTGCA GTCTATGCTG  
TTCAGGTGCG CTGTAAGAGG CTAGATGGAC TGGGATATTG GAGTAATTGG AGCAATCCAG  
CCTACACAGT TGTCATGGAT ATAAAAGTTC CTATGAGAGG ACCTGAATTT TGGAGAATAA  
TTAATGGAGA TACTATGAAA AAGGAGAAAA ATGTCAC TTTTGGGAAG CCCCTGATGA  
AAAATGACTC ATTGTGCAGT GTTCAGAGAT ATGTGATAAA CCATCATACT TCCTGCAATG  
GAACATGGTC AGAAGATGTG GGAAATCACA CGAAATTCAC TTTCTGTGG ACAGAGCAAG  
CACATACTGT TACGGTTCTG GCCATCAATT CAATTGGTGC TTCTGTTGCA AATTTTAATT  
TAACCTTTTC ATGGCCTATG AGCAAAGTAA ATATCGTGCA GTCCTCAGT GCTTATCCTT  
TAAACAGCAG TTGTGTGATT GTTTCCTGGA TACTATCACC CAGTGATTAC AAGCTAATGT  
ATTTTATTAT TGAGTGGA AAAAATCTTAATG AAGATGGTGA AATAAAATGG CTTAGAATCT  
CTTCATCTGT TAAGAAGTAT TATATCCATG GTAAGTTTAC TATACTT

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTAAGTTATT TGNNNNNATA TCCTAACAG

29

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## (2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GTAAGCATTG GCNNNNNTTT TAAATTCAG

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GTAAGTACCA AANNNNNTTT TCAATATAG

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GTAAGTTATG CANNNNNTTT TTCCTTAAG



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## (2) INFORMATION FOR SEQ ID NO:19:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GTAAGTATAT TTNNNNAATA TTTAACAG

28

## (2) INFORMATION FOR SEQ ID NO:20:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GTAGGTTATG TANNNNNCCC TCATTACAG

29

## (2) INFORMATION FOR SEQ ID NO:21:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GTAAGAAAAC AGNNNNNTGT TTCAAATAG

29

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## (2) INFORMATION FOR SEQ ID NO:22:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

10

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

15

GTACGTATTA TTNNNNNTAT CTTTAAAG

29

## (2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

25

## (ii) MOLECULE TYPE: cDNA

30

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTATGTCAAG CTNNNNNAAA AATTCTAG

29

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- 40 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

45

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

50 GTACCTTTTA CTNNNNNCTT ATTTTACAG

29

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## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

10

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

15

GTCTGCAGAG ATNNNNNGTC ATTTTGCAG

29

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

25

## (ii) MOLECULE TYPE: cDNA

30

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GTATTCCCAA TTNNNNNTAT TTACTACAG

29

## 35 (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- 40 (A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

45

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

50 GTATTCCCAA TTNNNNNTAT TTACTACAG

29

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## (2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GTAAGTTTAC TANNNNNTTT TCTCCTCAG

## (2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GTAAAAATTA TANNNNNTTT CTTTTTCAG

## (2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 29 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GTATTGTACT TGNNNNNTAT CCTTTGTAG

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## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GTTGCTTTTT CANNNNNTTA TCTAAACAG

29

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GTACATTTGT CTNNNNNCTT TTCTTTTAG

29

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GTATCCAGTG TTNNNNNCTT TTAAACAG

29

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## CLAIMS

1. An OB receptor protein preparation  
5 containing an OB receptor protein, optionally in a  
pharmaceutically acceptable formulation, said OB  
receptor protein having part or all of the amino acid  
sequence according to Seq. ID No. 1 and one or more of  
the biological properties of naturally occurring OB  
10 receptor protein.
2. An OB receptor protein preparation  
containing an OB receptor protein, optionally in a  
pharmaceutically acceptable formulation, wherein said OB  
15 receptor protein amino acid sequence is selected from  
among amino acid sequences (according to Seq. ID No. 1):
  - (a) 1-896;
  - (b) 22-896 optionally with an N-terminal  
methionyl residue;
  - 20 (c) 23-896 optionally with an N-terminal  
methionyl residue;
  - (d) 29-896 optionally with an N-terminal  
methionyl residue;
  - (e) 1-839;
  - 25 (f) 22-839 optionally with an N-terminal  
methionyl residue;
  - (g) 29-839 optionally with an N-terminal  
methionyl residue;
  - (h) 1-841;
  - 30 (i) 22-841 optionally with an N-terminal  
methionyl residue;
  - (j) 23-841 optionally with an N-terminal  
methionyl residue;
  - (k) 29-841 optionally with an N-terminal  
35 methionyl residue;
  - (l) 1-891;

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(m) 22-891 optionally with an N-terminal methionyl residue;

(n) 23-891 optionally with an N-terminal methionyl residue;

5 (o) 29-891 optionally with an N-terminal methionyl residue;

(p) of subparts (l) through (o) further having the C-terminal amino acids, beginning at position 892, of OB receptor B (Seq. ID No. 3) or C (Seq. ID No. 5); and,

10 (q) a chemically modified derivative of any of subparts (a) through (p).

3. An OB receptor protein preparation of claim 2 wherein said OB receptor protein is further selected from among the OB receptor proteins of subparts (l) through (o) further having the C-terminal amino acids, beginning at position 892, of OB receptor protein D (Seq. ID No. 7).

20

4. An OB receptor protein preparation of claim 2 wherein said OB receptor protein is further selected from among the OB receptor proteins of subparts (l) through (o) further having substituted the C-terminal amino acids, beginning at position 799, G K F T I L (Seq. ID No. 13).

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5. An OB receptor protein preparation according to any of claims 1 through 4, wherein the extracellular domain of said OB receptor protein is modified, said modification selected from among:

- (a) deletion of all or part of the random coil domain;
- (b) modification of one or both "WSXWS" boxes by substitution of the first serine with another amino acid;
- (c) modification of one or both "WSXWS" boxes by substitution of the last serine with another amino acid; and
- (d) modification of one or both "WSXWS" boxes by substitution of the first tryptophan with another amino acid.

6. A DNA molecule encoding an OB receptor protein according to any of claims 1-5 selected from the group consisting of:

- (a) the DNA sequences set forth in Seq. ID nos. 2, 4, 6, 8, 11, 12, and 14;
- (b) a DNA which selectively hybridizes to a DNA of subpart (a); and
- (c) a DNA which, but for the degeneracy of the genetic code would hybridize to a DNA of subpart (a) or (b).

7. A biologically functional viral or plasmid vector containing a DNA of claim 6.

8. A procaryotic or eucaryotic host cell containing the vector of claim 7..

9. A host cell modified so that expression of endogenous OB receptor protein is enhanced.



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10. A host cell of claim 9 which is an isolated human host cell.

5           11. A process for producing an OB receptor protein comprised of culturing, under suitable conditions, a host cell according to any of claims 8, 9 or 10, obtaining the OB receptor produced, and optionally preparing a pharmaceutical composition  
10 containing said OB receptor.

          12. A method of treating an individual for a therapeutic disorder selected from among obesity, diabetes, high blood lipid levels, and high cholesterol  
15 levels comprised of administering a therapeutic amount of an OB receptor protein preparation containing an OB receptor protein according to any of claims 1-5, or produced by the process according to claim 11.

20           13. A method of treating an individual for weight loss or weight maintenance for solely cosmetic purposes comprised of administering an effective amount of an OB receptor preparation containing an OB receptor protein according to any of claims 1-5, or produced by  
25 the process according to claim 11.

          14. Use of an OB receptor protein according to claims 1-5, or produced by the process of claim 11, for manufacturing a medicament for the treatment of  
30 obesity, diabetes, high blood lipid levels, or high cholesterol levels.

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15. An OB protein/OB receptor protein complex preparation, containing an OB protein moiety and an OB receptor protein moiety, optionally in a pharmaceuti-  
5 cally acceptable formulation, wherein:

(a) said OB receptor protein is selected from among those set forth in any of claims 1 and 2;

(b) said OB protein moiety is selected  
10 from among:

(i) a naturally occurring OB protein; and,

(ii) a non-naturally occurring OB protein, analog or derivative thereof.

15

16. An OB protein/OB receptor protein complex preparation of claim 15 wherein said OB receptor protein is selected from among those set forth in any of claims 3, 4, and 5.

20

17. A method of treating an individual for a therapeutic disorder selected from among obesity, diabetes, high blood lipid levels, and high cholesterol levels comprised of administering a therapeutic amount  
25 of an OB protein/OB receptor protein complex preparation of claims 15 or 16.

18. A method of claim 17 wherein said OB protein/OB receptor protein complex preparation is  
30 formed in vivo by administering, into a patient, a first population of cells expressing an OB protein, and a second population of cells expressing an OB receptor protein.

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19. A method of treating an individual for weight loss or weight maintenance for solely cosmetic purposes comprised of administering a therapeutic amount of an OB protein/OB receptor protein complex preparation containing an OB receptor protein moiety according to any of claims 1-5, or produced by the process according to claim 11.
20. Use of an OB protein/OB receptor protein complex preparation, according to claims 15 or 16, for manufacturing a medicament for the treatment of obesity, diabetes, high blood lipid levels, or high cholesterol levels.

## A. CLASSIFICATION F SUBJECT MATTER

IPC 6 C12N15/12 C12N5/10 C07K14/715 C07K16/28 C12Q1/68  
G01N33/50 A61K38/17 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CELL, vol. 83, 29 December 1995, pages 1263-1271, XP000602068 TARTAGLIA, L.A., ET AL. : "IDENTIFICATION AND EXPRESSION CLONING OF A LEPTIN RECEPTOR, OB-R" see the whole document & EMBL SEQUENCE DATA LIBRARY, 30 December 1995, TARTAGLIA, L.A., ET AL. : "IDENTIFICATION AND EXPRESSION CLONING OF A LEPTIN RECEPTOR, OB-R" ACCESSION No. U43168 ---	1,3,6-8
P,X	WO 96 08510 A (PROGENITOR INC) 21 March 1996 see the whole document ---	1,2,6-11
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

28 April 1997

Date of mailing of the international search report

07. 05. 97

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## INTERNATIONAL SEARCH REPORT

Int. Patent Application No  
PCT/US 97/00128

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>NATURE MEDICINE, vol. 2, no. 5, May 1996, pages 585-589, XP0002019361 CIOFFI, J.A., ET AL. : "NOVEL B219/08 RECEPTOR ISOFORMS: POSSIBLE ROLE OF LEPTIN IN HEMATOPOIESIS AND REPRODUCTION" see the whole document &amp; EMBL SEQUENCE DATA LIBRARY, 26 April 1996, HEIDELBERG, GERMANY, CIOFFI, J.A., ET AL. : "NOVEL B219/08 ISOFORMS: POSSIBLE ROLE OF LEPTIN IN HEMATOPOIESIS AND REPRODUCTION" ACCESSION No.s U52912, U52913; U52914 ---</p>	1,2,6-8
P,X	<p>CURRENT BIOLOGY, vol. 6, no. 9, 1 September 1996, pages 1170-1180, XP000673008 BENNETT, B.D., ET AL.: "A ROLE FOR LEPTIN AND ITS COGNATE RECEPTOR IN HEMATOPOIESIS" see the whole document &amp; EMBL SEQUENCE DATA LIBRARY, 7 September 1996, HEIDELBERG, GERMANY, BENNETT, B.D., ET AL. : "A ROLE FOR LEPTIN AND ITS COGNATE RECEPTOR IN HEMATOPOIESIS" ACCESSION No. U66496 ---</p>	1-3,6-8
P,X	<p>BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 224, no. 2, 16 July 1996, pages 597-604, XP002029745 IIDA, M., ET AL. : "SUBSTITUTION AT CODON 269 (GLUTAMINE - PROLIN) OF THE LEPTIN RECEPTOR (OB-R) cDNA IS THE ONLY MUTATION FOUND IN THE ZUCKER FATTY (fa/fa) RAT" see the whole document &amp; EMBL SEQUENCE DATA LIBRARY, 12 June 1996, HEIDELBERG, GERMANY, IIDA, M., ET AL. : "PHENOTYPE-LINKED AMINO-ACID ALTERATION IN LEPTIN RECEPTOR cDNA FROM ZUCKER FATTY (fa/fa) RAT" ACCESSION No. D84125 --- -/--</p>	1,6-8

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>CELL, vol. 84, 9 February 1996, pages 491-495, XP002029746 CHEN, H., ET AL . : "EVIDENCE THAT THE DIABETES GENE ENCODES THE LEPTIN RECEPTOR: IDENTIFICATION OF A MUTATION IN THE LEPTIN RECEPTOR GENE IN db/db MICE" see the whole document &amp; EMBL SEQUENCE DATA LIBRARY, 11 February 1996, HEIDELBERG, GERMANY, CHEN,H., ET AL . : "EVIDENCE THAT THE DIABETES GENE ENCODES THE LEPTIN RECEPTOR: IDENTIFICATION OF A MUTATION IN THE LEPTIN RECEPTOR GENE IN db/db MICE" ACCESSION No. U46135 -----</p>	1,6-8

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/00128

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608510 A	21-03-96	AU 3419495 A	29-03-96
		CA 2176463 A	21-03-96
		EP 0730606 A	11-09-96
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